Perspective Report Series 8

PERSPECTIVES IN ORGANIC SYNTHESIS

G. MEHTA AND M. NAGARAJAN

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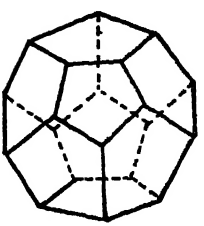
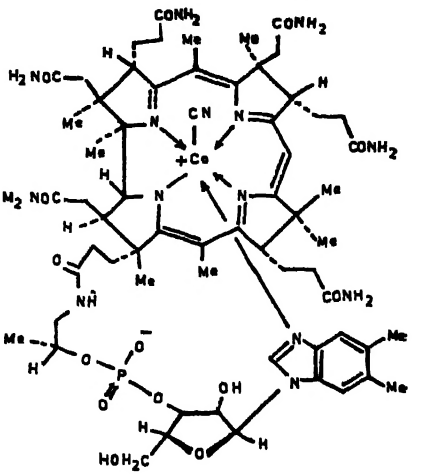
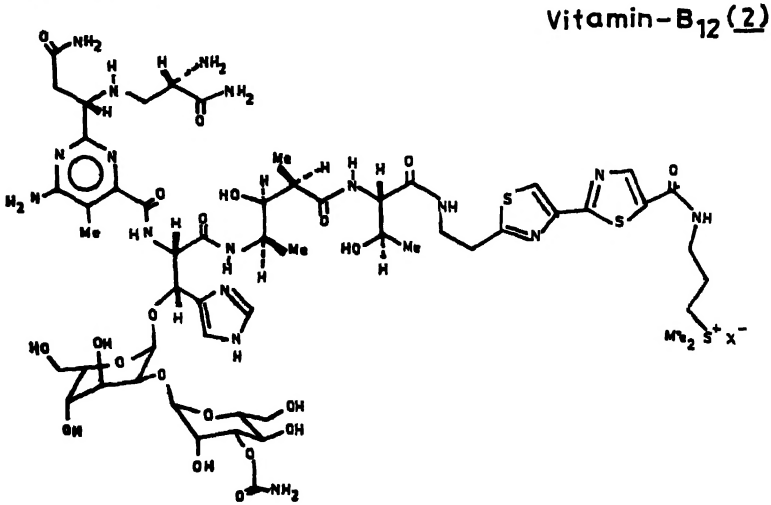
quite hopelessly complex, particularly in view of its plethora of asymmetric centres....' (R. B. Woodward in 'Perspectives in Organic Chemistry,' Ed. Sir A. R. Todd, 1956, p. 160). Twentyfive years after making this dismal prognosis, Woodward himself, in 1981, annihilated erythromycin in a massive, ingenious assault (*vide infra*).



Dodecahedrane(1)

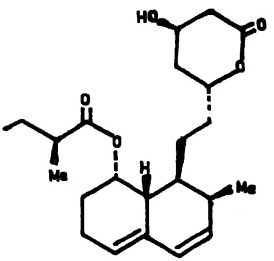


Vitamin-B_{12} (2)

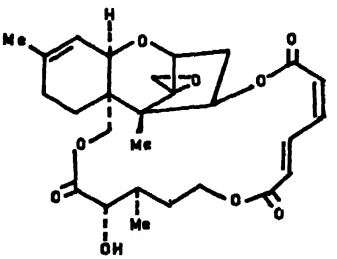


Bleomycin-A_2 (3)

Some of the outstanding achievements of the past few years leading to the total synthesis of dodecahedrane (1), [3] vitamin-B_{12} (2), [4] bleomycin-A_2 (3),[5] verrucarin-A (4)[6] and compactin (5)[7] bear ample testimony to the state-of-the-art. Many more impressive accomplishments of total synthesis are described in this sequel later on.



Compactin(5)

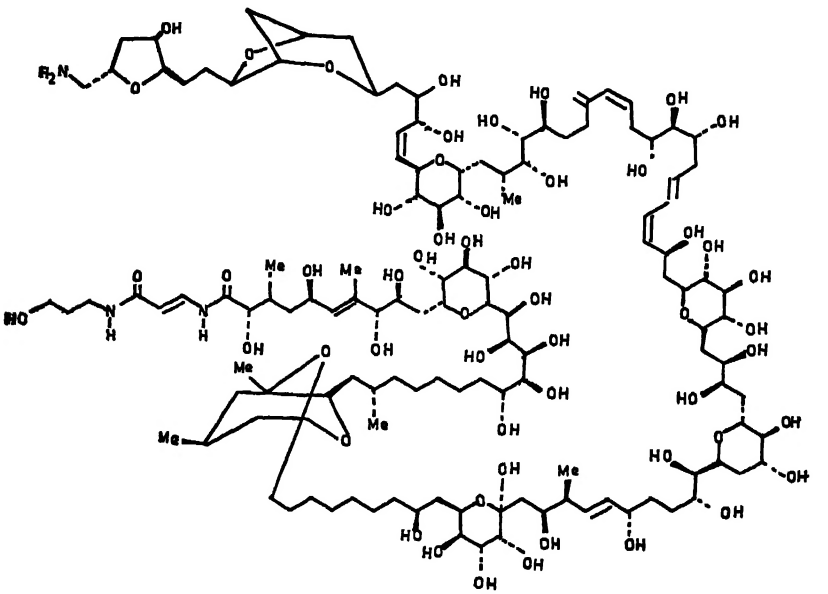


Verrucarin A (4)

There are many motivations for undertaking a synthetic venture. These range from the mere intellectual challenge of assembling a complex array (eg., 2, 3) or an aesthetically pleasing framework (eg, 1) to the development of practical approaches to the syntheses of drugs, polymers, pesticides and the like, which may lack molecular complexity but are of every day use and benefit to mankind. At times, a synthetic exercise is also undertaken either to arrive at or for providing unambiguous proof for the structures of natural products. The elucidation of the complete stereostructure of palytoxin (6) by Kishi, Uemura and Hirata is a brilliant demonstration of this facet of synthetic activity.[8]

It can be seen from the foregoing description that present day synthetic activity covers a vast arena. This account, therefore, attempts to focus attention on molecules, methodologies and reagents that occupy the centre stage in organic synthesis to-day and have a promising tomorrow. In the first part, this article presents a bird's eye view of broad areas and individual compounds that have attracted extensive contemporary interest from synthetic chemists. The second part presents some of the new synthetic strategies which are currently in vogue and have been specifically developed to meet

these challenges. Both the parts have been spiced with some stimulating examples from the literature of the past 3–5 years and the coverage is upto October 1983! Due to the constraints of space, we had to be choosy and have made a conscious effort to illustrate our article with themes that appealed to us most for their originality and future applications. There could be some notable omissions in our account for which we take full responsibility. After all, this article is meant to reflect the authors' perspective!



Palytoxin (6)

2. The Present Scene

The wide variety of reactions and methodologies available to the synthetic organic chemist today enable him to take on more and more complex molecules as targets for synthesis. Simultaneously, attention is also being paid to molecules, which though not very complex, are important as models for areas of contemporary interest such as energy storage, enzymatic reactions, superconducting

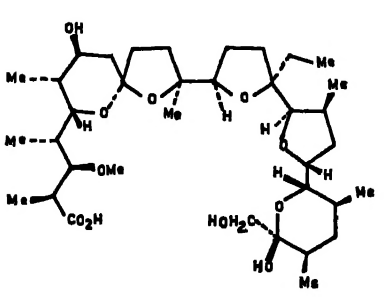
materials and the like. A third area of interest is concerned with the development of new synthetic reagents capable of effecting reactions with a high degree of stereo-, regio-, and chemo-selectivity. An overview of the current trends in each of the areas mentioned above is presented in the subsequent paragraphs.

I. Total Synthesis of Natural Products

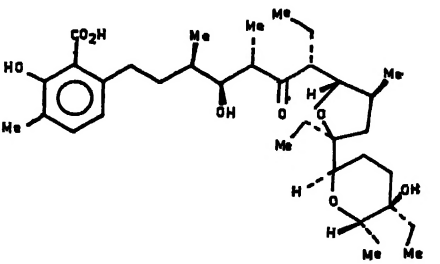
In the evolution of organic synthesis over the years, certain classes of compounds have been in the lime-light at each stage of its progress. For example, the premier position occupied by the steroids in the forties and fifties yielded place to the complex terpenoids and alkaloids which were, in turn, displaced by the prostanoids. Today, the emphasis is primarily on ionophore antibiotics, macrolides and related compounds, polycyclopentanoids, anthracyclines and eicosanoids. The reasons for their popularity as synthetic targets, the structural and stereochemical complexities involved in their synthesis and the approaches developed to tackle such difficulties are briefly highlighted below.

Ionophore Antibiotics

For many years, the mechanism of ion transport across biological membranes was a little understood phenomenon. In the sixties, crown ethers were synthesized and it was shown that these had the ability to encapsulate sodium, potassium and calcium ions which are of biological interest.[9] About the same time, some antibiotics were isolated from various microbial sources and were found to bind

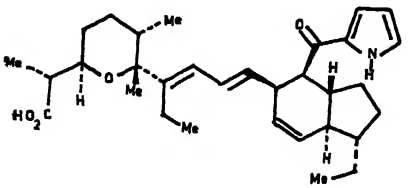


Monensin (7)[10]

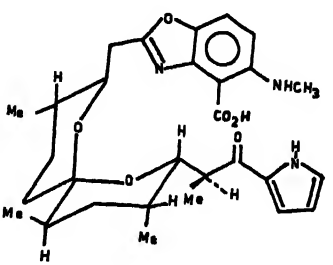


Lasalocid-A (8)[11]

metal ions in a manner similar to crown ethers, thus suggesting a role for these compounds in the transport of metal ions in biological systems. The more prominent of the ionophore antibiotics are monensin (7),[10] lasalocid-A (8),[11] X-14547-A (9),[12] and A-23187 (10),[13] among others. Apart from their intriguing structures, these antibiotics possess interesting biological properties. Monensin (7) is active in the transport of sodium ions and finds use as an antibacterial and antifungal agent in veterinary medicine. A-23187 (10) is involved in calcium ion transport and as the calcium ions play an ubiquitous role in biological systems, the importance of A-23187(10) can hardly be overlooked. Lasalocid-A (8) and X-14547-A (9) are capable of complexing and transporting both monovalent and divalent cations, thereby displaying dual selectivity.



X-14547-A (9)[12]



A-23187 (10)[13]

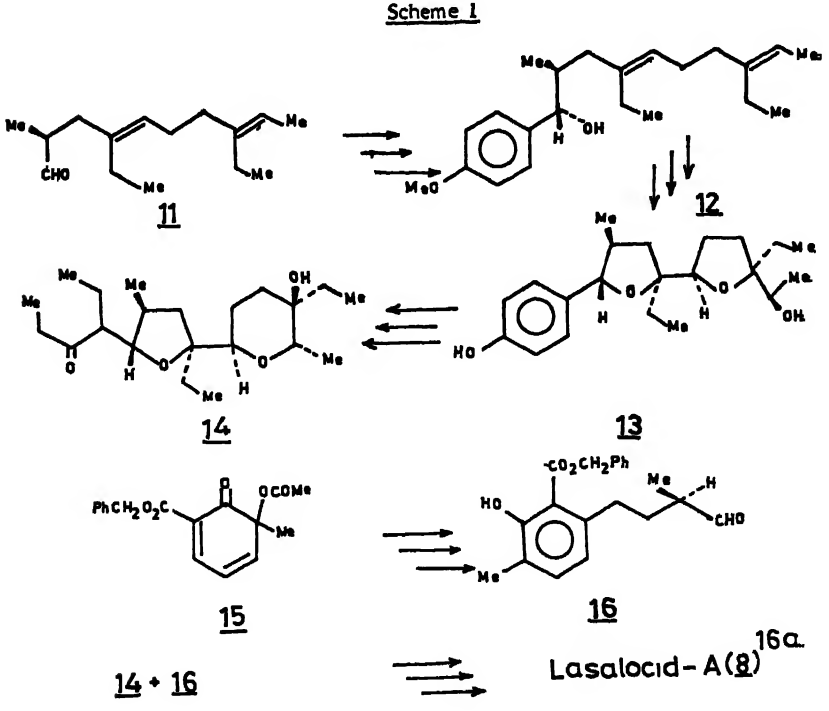
A look at the structures of these four typical ionophore antibiotics 7-10 immediately gives an idea of their complexity. An important feature present in these antibiotics is the relatively large number of asymmetric centres located along the carbon chain at non-ring positions. The combination of this unique structural feature and the high degree of functionality present in them together with their interesting biological properties have made them popular and challenging synthetic targets.

The difficulties involved in the total syntheses of this magnitude are obvious. Monensin, for example, has 17 asymmetric centres and is one of 131, 072 possible stereoisomers! It becomes almost obligatory, therefore, to ensure a very high degree of stereochemical control at every chiral centre during the execution of the synthesis.

As pointed out earlier, many of the chiral centres are at acyclic positions and hence the stereochemical control has to be exercised through acyclic stereoselection Inherently, this process is more difficult than cyclic stereoselection, where the rigidity of the ring system and conformational preferences exert a greater influence. In addition, remote control of stereochemistry is also required due to presence of some isolated chiral centres. Finally, the conformations of the various tetrahydropyran and tetrahydrofuran rings are to be reckoned with as well. In the ultimate analysis, such molecular structures are formidable targets indeed.

A number of ingenious methods have been developed to tackle the difficulties enumerated above. Acyclic stereoselection *via* aldol condensation using lithium[14] and boron[15] enolates has enablea the achievement of a very high degree of stereocontrol (*vide infra*). Judicious use of different chiral synthons, especially those derived from carbohydrates, has been useful in setting up the correct

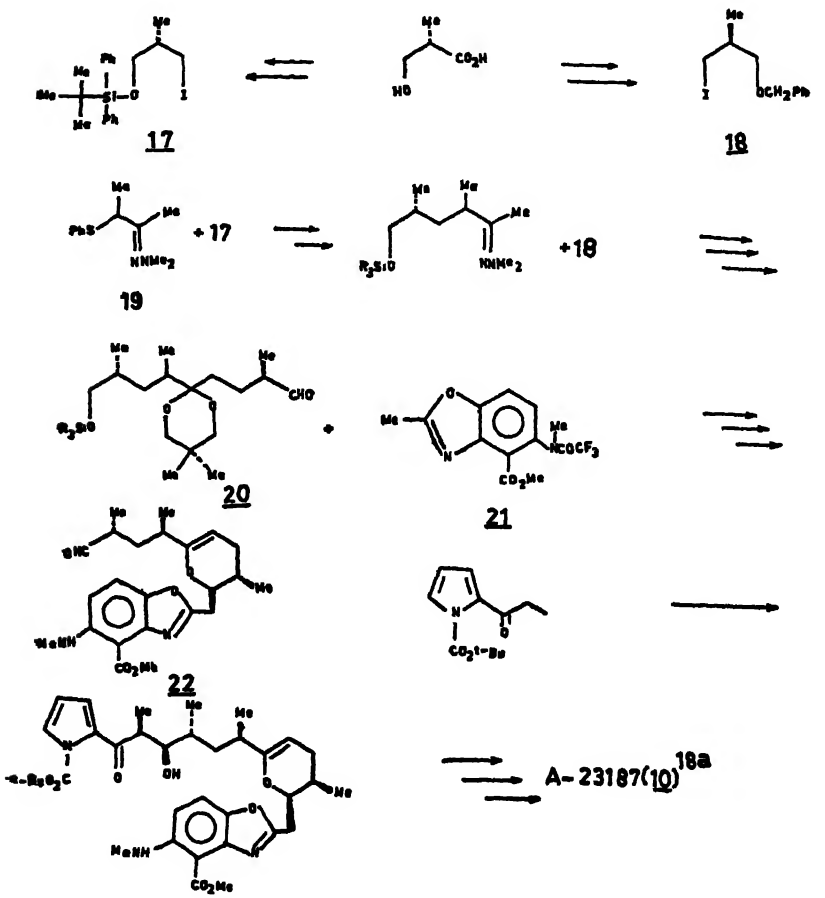
Scheme 1



stereochemistry in lasalocid-A (8)[16] and X-14547-A (9)[17]. A bicyclic template was employed to set up the requisite stereochemistry in A-23187 (10).[18b] Chelation controlled addition played an important role in the total synthesis of monensin. (7)[19b]

A few key steps from the syntheses of 8–10 are shown in Schemes 1, 2 and 3. In the Kishi synthesis[16a] of lasalocid-A (8) the dienal 11 is converted to 12 through a series of standard reactions and resolved. The optically active alcohol 12 is now cyclised inframolecularly to the required bistetrahydrofuran derivative 13 and then

Scheme 2

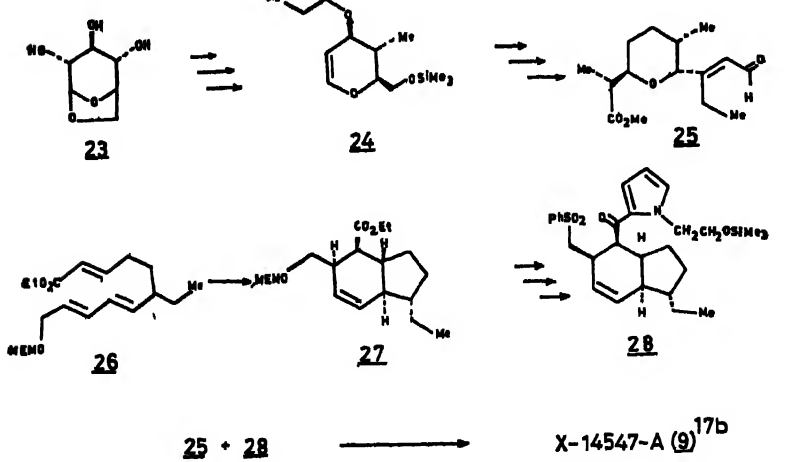


rearranged to 14, which constitutes the 'right hand fragment' of 8. The aromatic aldehyde 16 which is the 'left hand fragment' is synthesized from dienone 15 and finally the two halves 14 and 16 are assembled *via* an aldol condensation, Scheme 1.

For the synthesis of A-23187 (10), Evans employed (S)-p-hydroxyisobutyric acid as the chiral starting material which was converted to 17 and 18. Sequential alkylation of the N,N-dimethylhdrazone 19 with 17 and 18 gave, after suitable manipulation, the aldehyde 20, which was condensed with the benzoxazole 21 to form 22. An aldol condensation and further transformations ultimately led to A-23187 (10), Scheme 2.

Ley, [17b] in his synthesis of X-14547-A (9), used a carbohydrate, laevoglucosan (23) as the chiral precursor and converted it to the allylic ester 24 which was subjected to the Ireland modification of the Claisen rearrangement to give 25. An intramolecular Diels-Alder reaction of 26 provided entry to hydrindane 27 which was resolved and converted to 28. Sulphone 28 was then condensed with aldehyde

Scheme 3

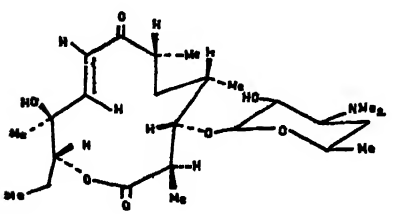


25 *via* a Julia reaction to generate the required diene unit present in X-14547-A (9), Scheme 3. The fact that such complex structures could be synthesized is a tribute to the versatility of organic reactions.[16-18]

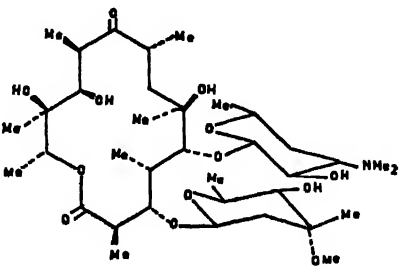
Finally, mention should be made of the attempts underway at the total synthesis of the marine toxin palytoxin (6).[8] The logistics involved in a synthetic effort of such a magnitude are too obvious to be mentioned.

Macrolides and Ansamycins

Closely related to the ionophore antibiotics in their complexity are the macrolide and ansamycin antibiotics. Macrolides are large ring lactones and usually carry a sugar residue. Typical examples are methymycin (29)[20] and the broad spectrum antibiotic erythromycin (30)[21] Ansamycins have an aliphatic bridge linking non-adjacent positions of an aromatic ring. The best known examples



Methymycin (29)[20]

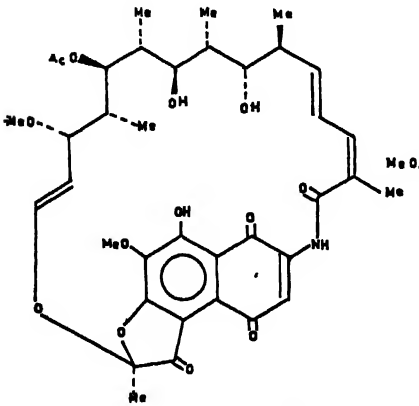


Erythromycin (30)[21]

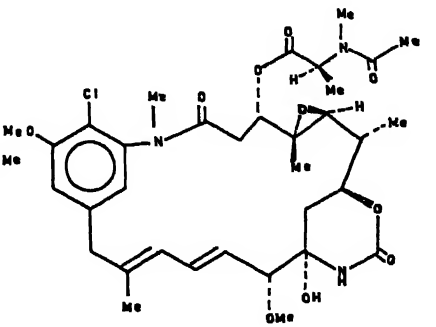
are the antitubercular agent rifamycin S (31),[22] which has a naphthalene nucleus, and the anticancer drug maytansine (32), having a benzene moiety.

Although the macrolide antibiotics are nearly three decades old and have been in clinical use for a long time, their formidable structural features precluded any attempts at their total syntheses until recently. Ansamycins are of comparatively recent vintage, but both rifamycin S (31), maytansine (32) and their congeners have gained considerable importance because of their extremely useful chemotherapeutic properties. In common with ionophore antibiotics, they are stereochemically very complex and endowed with novel structural elements. The methodology needed for their syntheses parallels that required for the syntheses of ionophore antibiotics; this is not unexpected, as the two classes of compounds abound in

chiral centres strung along a fairly long aliphatic chain and control of stereochemistry becomes the critical feature in their syntheses. Another special aspect of macrolide synthesis is the formation of



Rifamycin-S (31)[22]



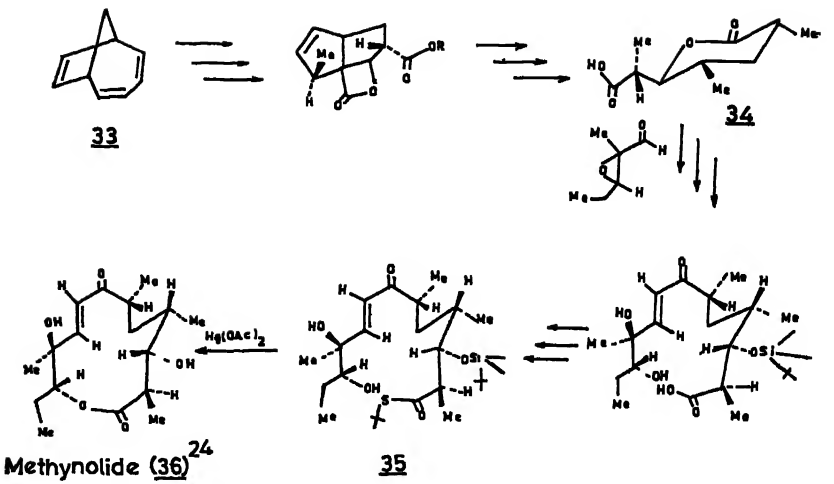
Maytansine (32)[23]

large ring lactones which is not a very feasible process entropically and considerable efforts were devoted to evolving methods to achieve this cyclisation under mild conditions and in good yield.

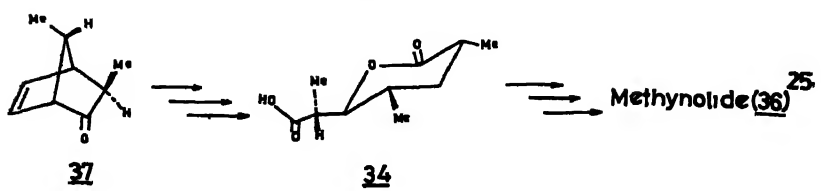
Methymycin (29) was the first macrolide antibiotic to be synthesized. The Prelog-Djerassi lactone 34 was prepared by Masamune[24] from a deceptively simple looking cyclic precursor 33 to control the stereochemistry and lactonization was effected using an activated ester approach (35→36). Methynolide (36) so obtained is readily convertible to methymycin (29), Scheme 4. Grieco[25] reported the synthesis of methynolide (36), also via the Prelog-Djerassi lactone (34). The stereochemistry in this case was controlled through a rigid, stereochemically well defined, bicyclo (2.2.1) heptane intermediate 37, Scheme 5.

Among the macrolide antibiotics, erythromycin (30) is important not only because of its broad spectrum antibiotic activity, but also because of its unique structure, containing a 14-membered lactone with 10 chiral centres and 2 sugar residues. The total synthesis of erythromycin 30 by Woodward[26] made elegant use of the 1,8-dithiadecalin ring system 38, both as a template to exert the required stereochemical control and as a masked methyl group equivalent. The approach, published after the demise of the Grand Master, has

Scheme 4



Scheme 5



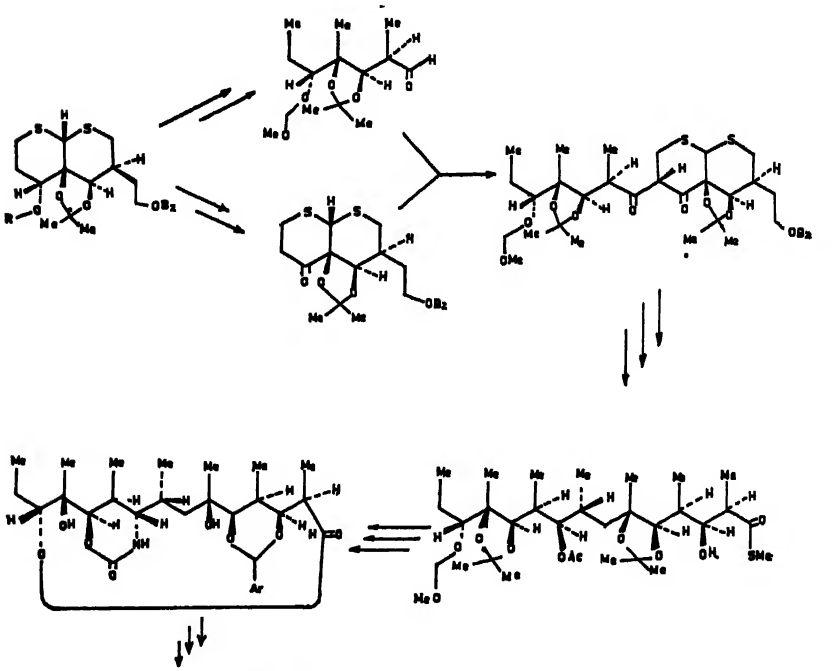
all the elements and aura of a Woodwardian classic, Scheme 6. In another elegant approach, the symmetry element present in the molecule has been used to advantage by Stork[27] to synthesize the acyclic precursor [39] from a common cyclic intermediate (40), Scheme 7.

Rifamycin S (31) is an important antitubercular agent and is used widely in India. Employing a sequence of nearly 50 steps, Kishi[28] has synthesized this compound, making liberal use of the recently developed asymmetric epoxidation of allylic alcohols *(vide infra)*. As in the ionophore and macrolide antibiotics, rigorous stereochemical control is a must in each step in order to generate the bridging chiral chain. A second method of setting up the requisite

stereochemistry along the chain depends heavily upon the recent advances in diastereoselective aldol condensations (*vide infra*) [25]

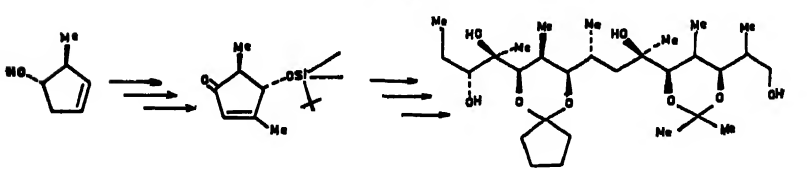
Among the compounds mentioned in this section, maytansine (32) is the only one to be obtained from a plant source.[23] Its paucity from natural sources and search for active analogs have stimulated efforts towards its synthesis. The presence of a cyclic urethane and

Scheme 6



Erythromycin (30)[26]

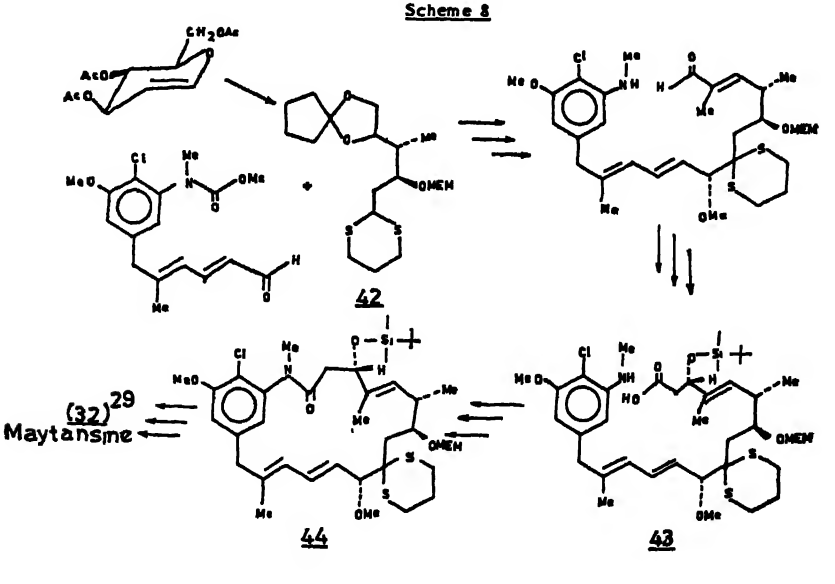
Scheme 7



40 Erythronolide precursor (39)[27]

a sensitive epoxide have to be borne in mind when devising a suitable synthesis of maytansine (32). Corey's synthesis employs macrolactamization as the key step to form the large ring amide (43→44); use of a carbohydrate precursor 41 to generate fragment 42 ensures the correct chirality as well, Scheme 8.[29] The second synthesis by Meyers consists of putting together the aromatic urethane 45, polyenic dibromide 46 and enantiomerically pure epoxide 47 and the critical lactamization was achieved in a novel way via a Wadsworth-Emmons type of a reaction (48→49), Scheme 9.[30] Once again, the power of organic synthesis is readily apparent in the design and execution of the syntheses of such complicated structures.[29-31]

Scheme 8

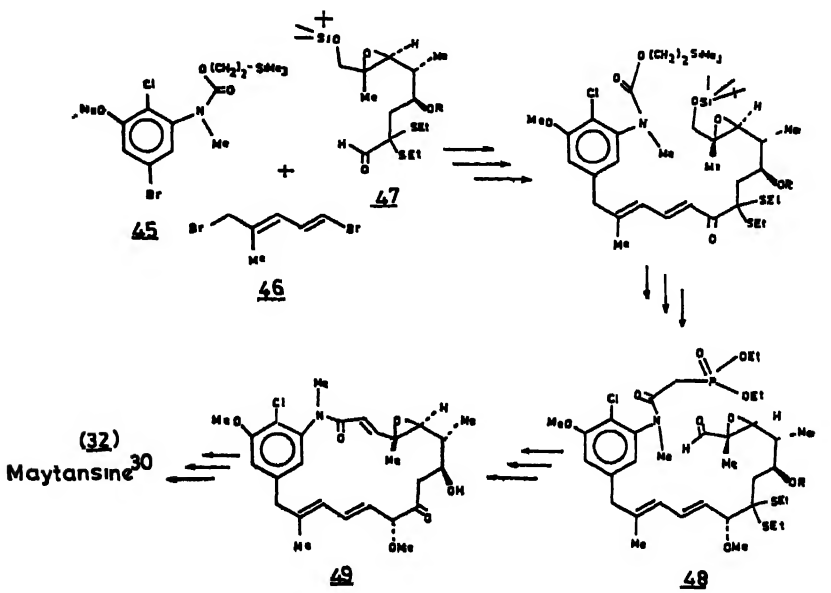


Polycyclopentanoids

Molecules with six-membered rings are almost ubiquitous in organic chemistry. Examples include benzenoid compounds and the various heterocycles as well as their saturated derivatives. Among natural products also, six-membered rings occur extensively, especially in steroids and to a lesser extent in terpenoids. On the other hand, five membered rings are relatively rare and gained currency particularly after the discovery of prostaglandins. It is

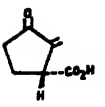
only in the past ten years or so that many natural products containing the polycyclopentanoid skeleton have been isolated. A few of them, like sarkomycin (50) and methylenomycin (51)[32] have only one cyclopentane ring, while many others consist of more than two or three cyclopentane moieties Typical examples include pentalenolactone (52),[33] quadrone (53),[34] coriolin (54),[35] isocomene (55),[36]

Scheme 9

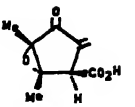


modhephene (56),[37] ikarugamycin (57),[38] and laurenene (58).[39] The interest in cyclopentanoid chemistry today is not only due to the wealth of structural variety present (which is considerable as can be seen) but also because of the interesting biological properties some of them possess. Thus, quadrone (53) and coriolin (54) exhibit significant tumor inhibiting properties and ikarugamycin (57) is an antibiotic.

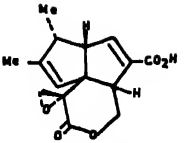
In devising the syntheses of polycyclopentanoids, the most important point to be borne in mind is the relative lack of methods for generating a five membered ring when compared to a cyclohexane system. Two powerful and general methods for generating six



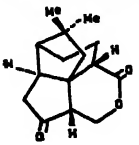
Sarkomycin(50)[32]



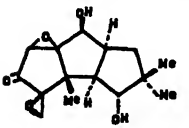
Methylenomycin(51)[32]



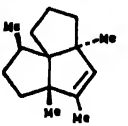
Pentalenolactone(52)[33]



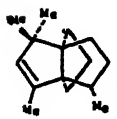
Quadrone(53)[34]

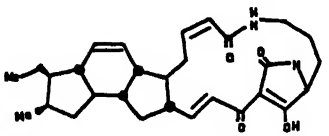


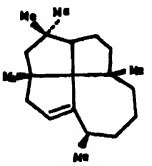
Coriolin(54)[35]



Isocomene(55)[36]







Modhephene(56)[37] Ikarugamycin(57)[38] Laurenene(58)[39]

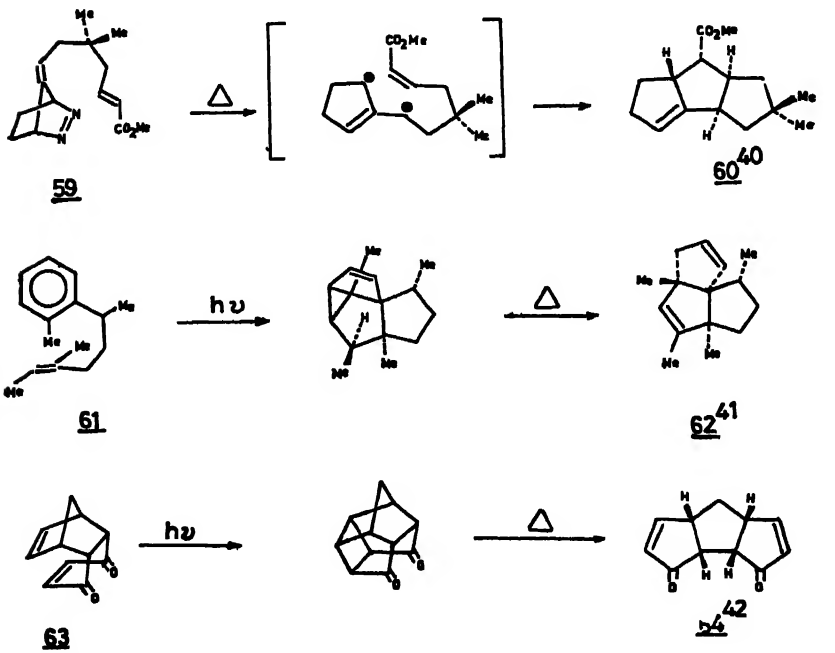
membered rings like the Diels-Alder reaction and the Robinson annulation are not adaptable for cyclopentane synthesis. The earlier syntheses of polycyclopentanoids were therefore based on repetitive annulation of a cyclopentane ring. The recent discoveries of many nutural products of the polycyclopentanoid type have resulted in the development of some new general methods. Mention should be made here of the 1,3-diyl trapping reaction (59→60),[40] meta-photocyclo-addition to arenes (61→62)[41] and the photo-thermal metathesis reaction (63→64)[42] as some of the recent strategies which address themselves to the specific task of diverse polycyclopentanoid synthesis, Scheme 10.

Anthracyclines

Anthracyclines have been known for a long time and constitute an important class of pharmacologically active compounds. In the middle sixties, two anthracyclines, daunomycin (65)[43] and adriamycin (66),[44] clinically known as daunorubicin and doxorubicin, respectively, were discovered and found to be active as broad spectrum

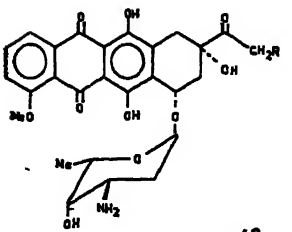
anticancer drugs. In conjunction with 5-fluorouracil, methotrexate, *cis*-platin and the like, these two compounds are widely employed in cancer chemotherapy. It is therefore no surprise that a tremendous amount of work is going on, around the world, in not only synthesizing daunomycin (65) and adriamycin (66), but also their analogues in the hope that more active and less toxic drugs can be obtained.

Scheme 10



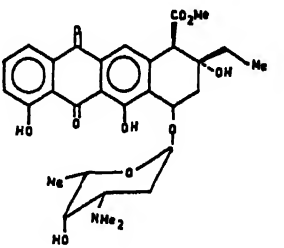
Structurally, these molecules are not very complex and comprise a tetracyclic aglycone and a sugar. Both portions have been synthesized by such a wide variety of methods that it is impossible to catalogue them here. The different strategies developed include a quinone reversed polarity approach (*vide infra*),[45] Diels-Alder reactions using a myriad combinations of dienes and dienophiles, and fairly standard methods of anthraquinone formation.[46] Significant

progress has also been made with analogues, especially the 4-demethoxy derivative of 65, which has superior chemotherapeutic value. Other anthracyclines of considerably lesser interest which have also attracted the attention of synthetic chemists include aklavin (67)[47] carminomycin (68)[48] and nogalamycin (69).[49]

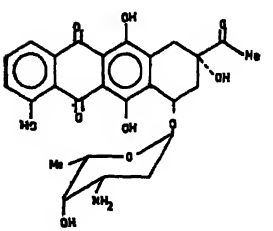


R = H Daunomycin (65)[43]

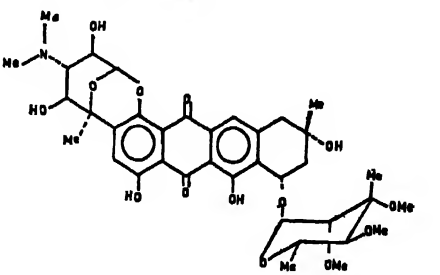
R = OH Adriamycin (66)[44]



Aklavin (67)[47]



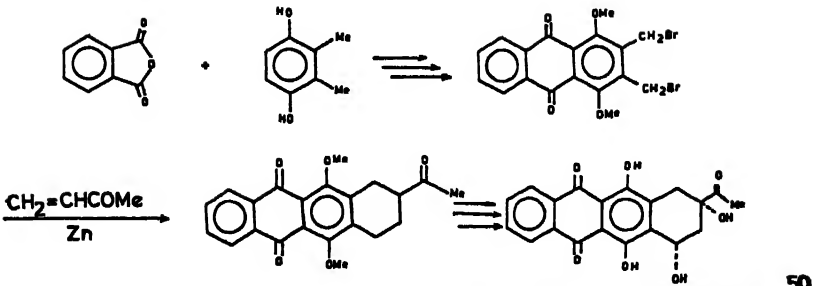
Carminomycin (68)[48]



Nogalamycin (69)[49]

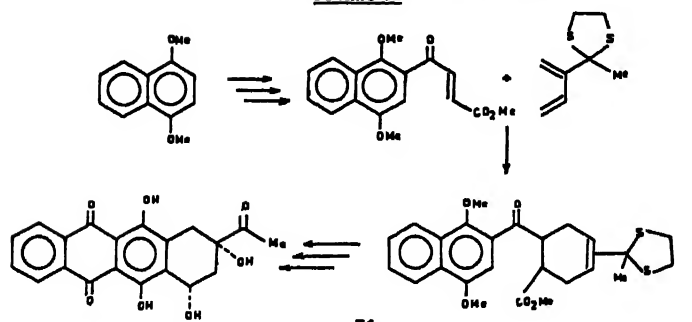
Of the many synthetic approaches to anthracyclines, only three are illustrated here. Cava's synthesis[50] of 70 uses the Diels-Alder reaction between a quinizarin and methyl vinyl ketone as the key step, Scheme 11. A second approach, also based on a Diels-Alder reaction, is due to Rama Rao[51] wherein the B ring is generated last, Scheme 12. Finally Kishi has reported[52] an asymmetric synthesis of aklavinone (71) in which the necessary chiral bias is supplied by an optically active acetal 72 participating in a silicon reagent 73 induced cationic alkylation, Scheme 13.

Scheme 11



4-Demethoxydaunomycinone (70)[50]

Scheme 12



4-Demethoxydaunomycinone (70)[51]

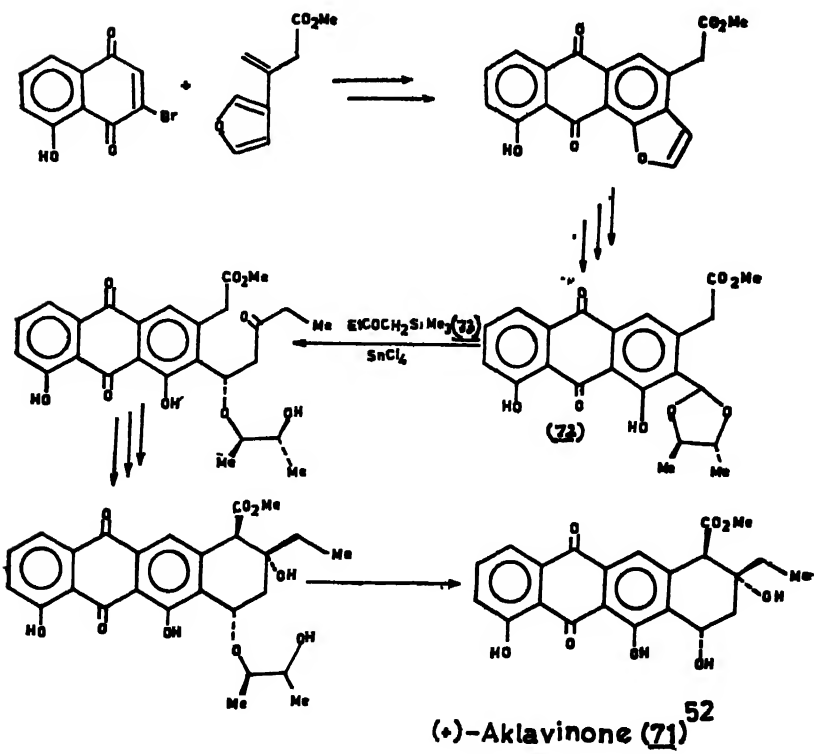
Numerous other approaches to the anthracyclines are available and an exhaustive list is given by Kelly.[46]

II. Synthesis of Theoretically Interesting Systems

Another facet of organic synthesis which has been of interest throughout the development of the subject is the preparation of molecules of theoretical importance and aesthetic appeal. Some of the molecules that attracted the organic chemists' attention in the fifties and sixties were cubane, adamantane, bullvalene, cyclopropenium and tropylium cations, cyclopentadienyl anion and various large ring annulenes.[53] As better and better synthetic methods developed, more and more difficult syntheses became possible. Thus,

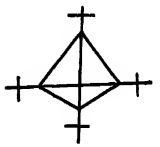
in the past few years tetra-t-butyltetrahedrane (74)[54] [1.1.1]-propellane (75),[55] pentaprismane (76)[56] [10,10]-betweenanene (77)[57] [5] peristylane (78),[58] superphane (79)[59] kekulene (80)[60] and tridecahelicene (81)[61] have all succumbed to the onslaught. The culmination, however, was the total synthesis of one of the platonic hydrocarbons, dodecahedrane (1) by Paquette[8] after a concerted and imaginative effort of nearly a decade. While such syntheses do not have any commercial or utility value, they illustrate very well the aesthetic appeal present in organic synthesis.

Scheme 13



III. 'Engineering' via Organic Synthesis

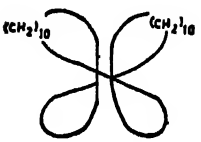
An important aspect of organic synthesis is the preparation of molecules which can be of specific use. Advantage of the synthetic power and versatility of organic chemistry is made use of to the full to



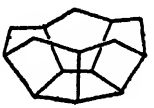
tetra-t-butyltetrahedrane (74)[54]

[111]-Propellane (75)[55]

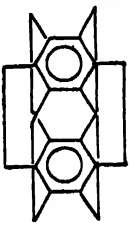
Pentaprismane (76)[56]



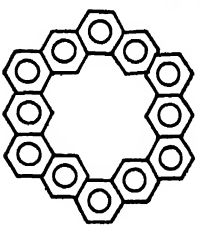
[10,10]-betweenanene (77)[57]



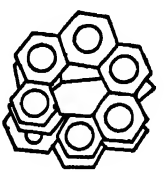
[5]-peristylane (78)[58]



Superphane (79)[59]



Kekulene (80)[60]



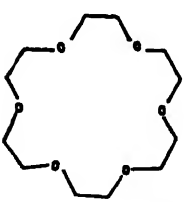
Tridecahelicene (81)[61]

'design' or 'engineer' compounds to meet certain specific requirements. In this broad category, three main areas have been in the forefront in the past few years namely enzyme mimics, organic metals and energy storage systems. A very important area which is not included here is that of drug design which finds extensive use in medicine and is of highly specialized interest.

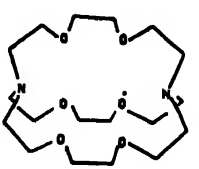
Enzyme Mimics

Scientists, and more so the organic-and bio-chemists have been fascinated for decades by the speed, efficiency and selectivity with which enzymes carry out various chemical transformations. As the understanding about the manner in which enzymes function increases, it becomes possible, at least in a crude way, to devise systems which can mimic the action of enzymes. These systems can be of two types, either of natural origin or of artificial make. The former include the well known behaviour of the various cyclodextrins, which provide 'cavities' within which different organic reactions occur.[62] Purely synthetic analogs are of more recent vintage and are objects of our interest here.

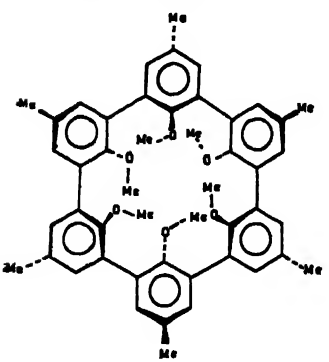
In the sixties and early seventies, crown ethers such as 82 and cryptands like 83 were synthesized and these displayed the ability to complex uniquely with various metal ions, depending upon the ionic size of the metal ion and size of the cavity of the ligand, thus constituting what can be termed as a 'lock and key' relationship.[9,63] Since



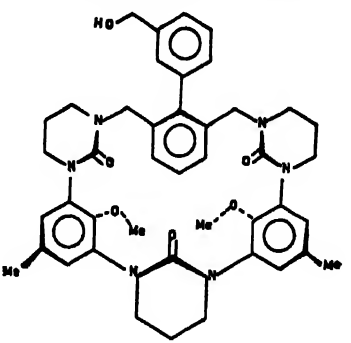
18-Crown-6 (82)[9]



[2.2.2] Cryptand (83)[63]



Cavitand (84)[64]

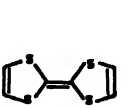


Cavitand (85)[65]

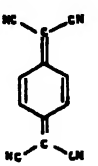
it is well known that the primary requirement for the efficient functioning of an enzyme is also the same, the attention of synthetic chemists was drawn to the task of synthesizing molecules which could behave more like an enzyme than the simple crown ethers, which exhibit only ion transport properties. Consequently, efforts are being made to duplicate enzymes by designing suitable molecules like cavitands 84[64] and 85,[65] which have already shown promising enzyme like reactivity.[66] This is an area in which the versatility of modern synthetic chemistry is being fully exploited and day may not be far off when totally synthetic enzymes will be designed and manufactured for designated purposes. This is clearly an area of future endeavours.

Organic Metals[67]

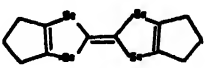
In 1973,[68] it was shown that the molecular complex between tetrathiafulvalene (86, TTF, 'donor') and tetracyano-p-quinodimethane (87, TCNQ, 'acceptor') exhibited electrical conduction comparable to metals at low temperatures (~60°K). This observation sparked an active search for other compounds of the same type with more favourable properties. Based on the theory of electrical conductivity in such molecular complexes, attempts were made



Tetrathiafulvalene (TTF) (86)



Tetracyanoquinodimethane (TCNQ) (87)



Hexamethylene-tetraselenafulvalene (HMTSF) (88)

to synthesize better donors and acceptors. Although TCNQ continues to remain the acceptor par excellence, the best donor to date is hexamethylenetetra-selenafulvalene (88, HMTSF) and the search is still on.

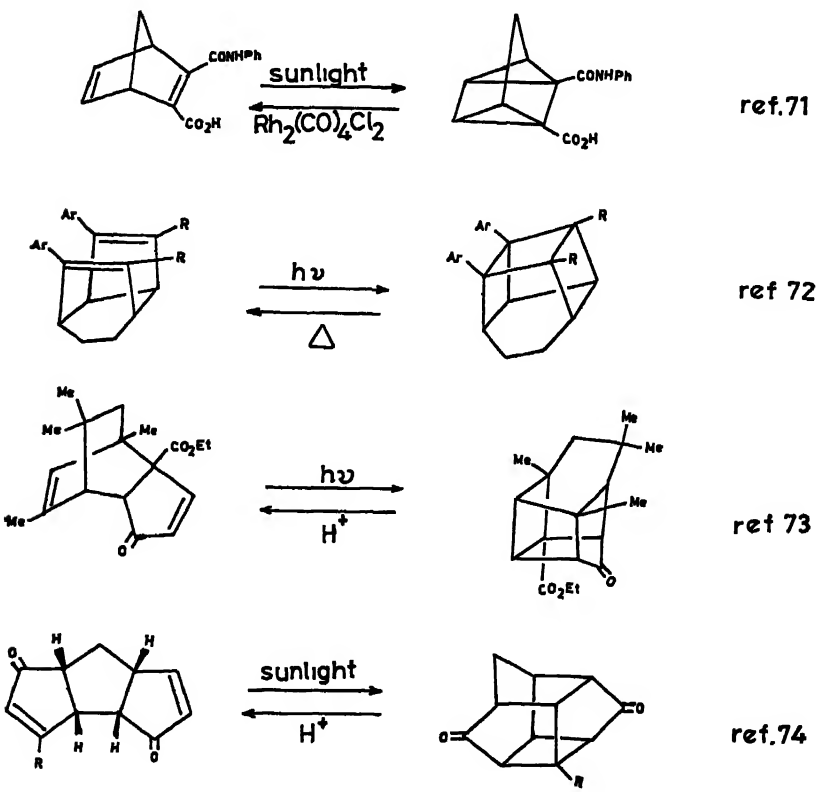
While the initial enthusiasm for an 'organic metal' has been somewhat dampened, it still continues to be an area of considerable

interest and the focus has now shifted to doping of systems like polypyrroles, polyphenylene sulphides and polyacetylenes with various Lewis acids like arsenic and antimony pentafluorides.[69]

Energy Storage Systems[70]

The rapidly diminishing reserves of fossil fuels have stimulated the search for alternative energy sources. These include geothermal, wind, biomass and solar energies. Amongst these, solar energy is a very attractive proposition due to its almost unlimited supply, especially in a country like ours which enjoys abundant sunshine. Solar energy can be converted to useful forms of energy in two

Scheme 14



different ways: by transforming it into electricity using solar cells and by storing it as chemical energy in certain energy rich organic molecules which can be induced to part with it on demand. Design of such systems which can reversibly store solar energy has drawn the attention of organic chemists in recent years.

In order to make the storage of solar energy as chemical energy feasible, a number of criteria have to be met and these have been discussed elsewhere. From the view point of an organic chemist, the basic requirement is a system in which a molecule on photochemical excitation by solar energy is transformed into an energy rich second molecule in high yield and with good quantum efficiency and the latter in turn can be converted to the former essentially completely in a clean reaction accompanied by the release of the stored energy. Obviously, for the system to be a good storage unit, the difference in energy between the two molecules should be as large as possible.

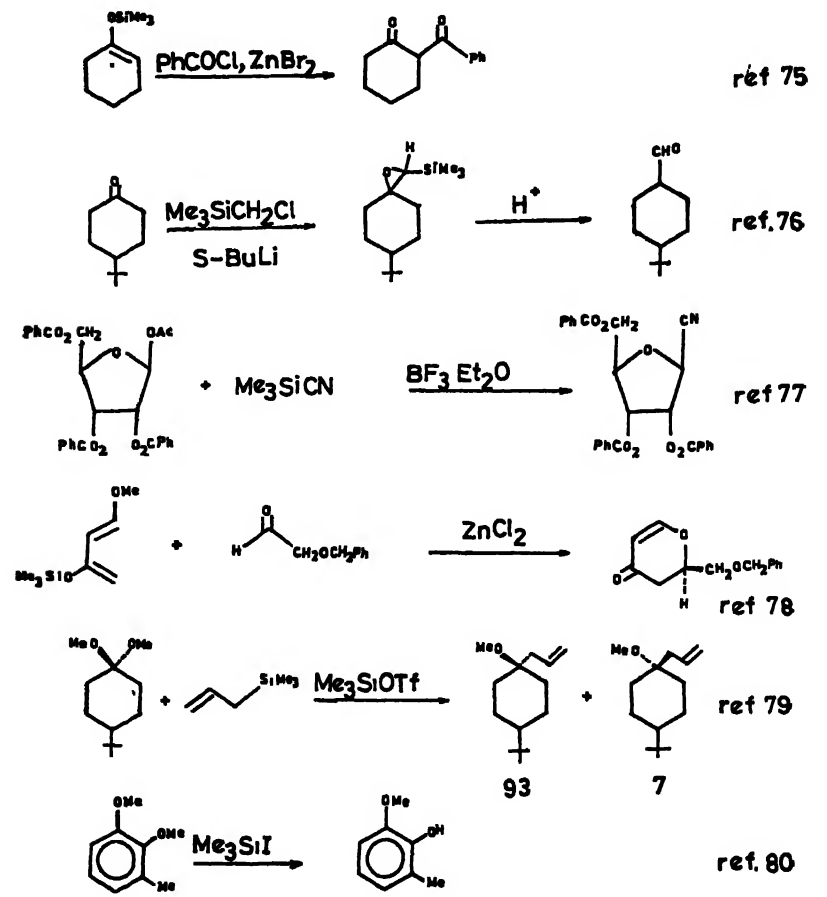
Some of the systems that have shown promising results are illustrated in Scheme 14.[71-74] In each instance, a seco-cage molecule is converted to a cage compound on photochemical excitation, the energy absorbed by the molecule being stored as chemical strain energy in the cage structure. Unravelling of the cage structure to the starting compound (usually induced by acid or mild heating) simultaneously releases the stored chemical energy as thermal energy. While the concept is a very simple one, a lot more research is necessary before a viable solar energy storage system based on the above principle can be developed.

IV. New Synthetic Reagents

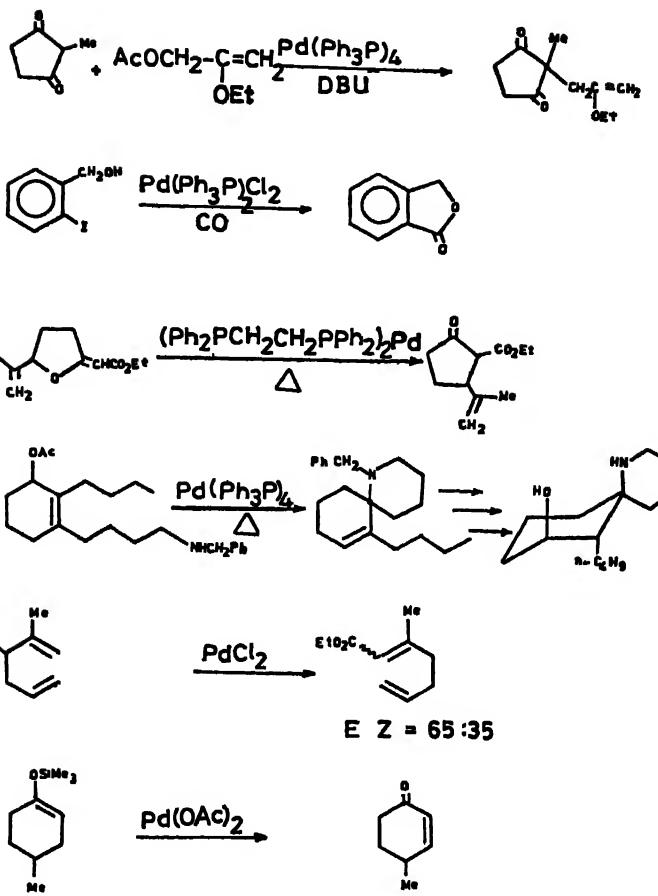
The ability of the synthetic organic chemist to synthesize complex molecules is governed to a large extent by the reactions at his disposal. As the complexity of a molecular structure increases, so does the need for reactions which can execute the desired transformations with a greater degree of stereo-, regio- and chemo-selectivity. In fact, the dividing line between the syntheses of complex molecules and devising new reactions is a very thin one, as the successful accomplishment of the former needs the latter and the versatility of the latter is measured by its application to the former. Therefore, the synthesis of molecules and the development of new reactions is a parallel exercise in organic chemistry.

Numerous methods have been developed for carrying out reactions more effectively and efficiently as well. Due to limitations of space, attention will be focussed here mainly on silicon, palladium and selenium based reactions. The choice of reagents is entirely arbitrary and is dictated by the fact that they are very versatile and therefore of widest use and interest. Schemes 15,16 and 17 illustrate some of the reactions based on silicon,[75–80] palladium[81–86] and selenium[87–91] containing reagents, respectively. In this context, it may

Scheme 15



Scheme.16



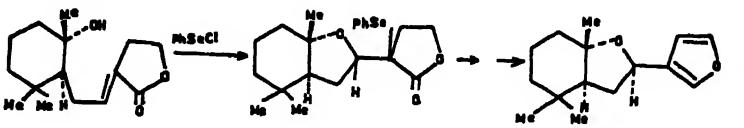
be mentioned that boron based reagents which have made a tremendous contribution to organic synthesis still continue to attract considerable attention.[92] New reagents involving transition metals like titanium and zirconium are also being increasingly used by organic chemists.[93]

3. New Synthetic Strategies

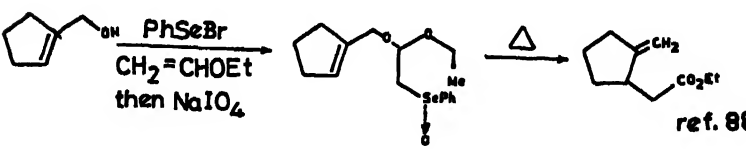
In the previous section, some of the areas, specific target molecules and reagents of current interest and activity in organic synthesis were

discussed. The successful planning and execution of a synthetic scheme, in most cases, hinges on one or two key reactions These may involve either creation of complex carbo- or heterocyclic frameworks and/or generation of requisite functionality with attendant stereo and regiochemical control. The choice of the key steps, as part of the overall synthetic strategy, therefore, depends not only

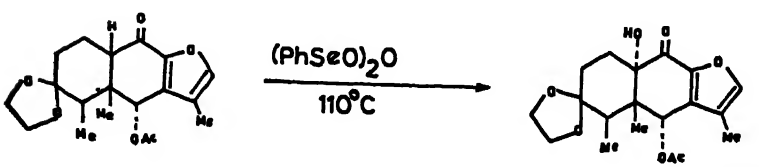
Scheme 17



Ancistofuran ref.87



ref. 88



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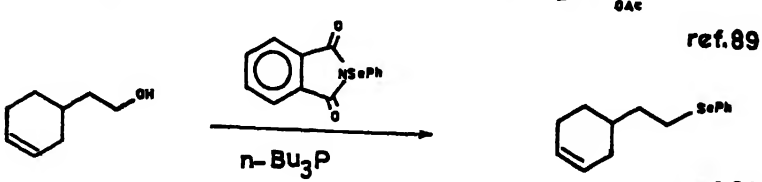

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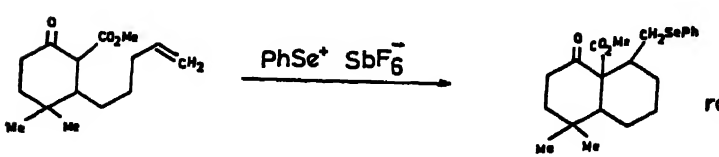


ref.91

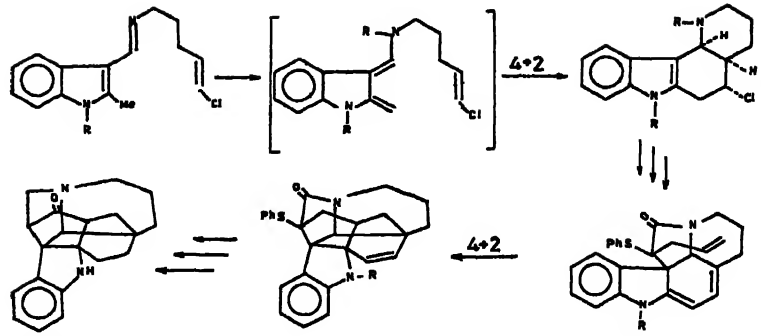
on the target molecule but more so on the availability of the state-of-the-art methodology, reactions and reagents. Consequently, in every decade of the growth of organic synthesis certain strategies have occupied pre-eminent position and remained fashionable. Let us illustrate this point further by looking at the evolutionary profile of steroid synthesis.[94] The marathon efforts of 1950's that culminated in the first total syntheses of several steroids relied heavily on intermolecular Diels-Alder reactions, Robinson annulation, Stobbe condensation, etc. as the key steps in generating the steroidal framework.[94] However, steroid synthesis in the next two decades became much shorter, more stereo-discriminatory using contemporary strategies based on intramolecular Diels-Alder reactions,[95] cationic polyene cyclisations,[96] intramolecular Michael additions, etc. and the approaches have been refined to such an extent that the tetracyclic steroid nucleus is now claimed to be accessible in a single pot operation![97]

In this section of our article, we discuss synthetic strategies that are dominating and stimulating the current synthetic efforts. Since such strategies are too numerous, in consonance with the thrust of organic synthesis over a wide front, we have made a conscious choice of those which in our opinion are versatile, conceptually novel and have a future. For convenient presentation, each strategy is discussed under a separate title with selected illustrations from recent literature and only the key step in each case is highlighted.

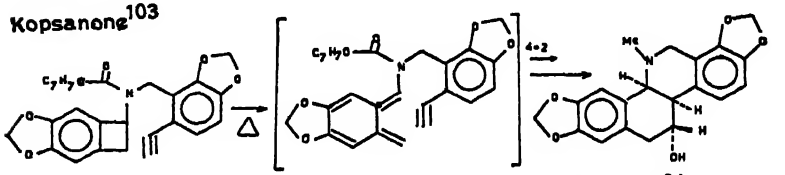
Intramolecular Diels-Alder and Related Reactions[98]

Ranking as one of the most useful of all reactions is the well known Diels-Alder reaction. Although reported for the first time over 50 years ago, various improvements and modifications over the years have ensured its continued popularity. A major advantage in this reaction is that the stereochemistry, and in some instances regiochemistry of the product is clearly defined with respect to that of the starting materials, thereby making it possible to obtain a product of known stereochemistry. The intramolecular version of the Diels-Alder reaction from an acyclic precursor can accomplish the same thing and simultaneously generate a bicyclic system. Exploitation of this variation became possible only after the availability of methods for the stereospecific syntheses of olefins so that precursors incorporating both the diene and the dienophile moieties could be

Scheme 18

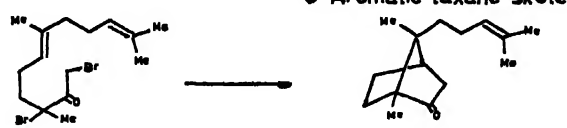


Kopsanone[103]

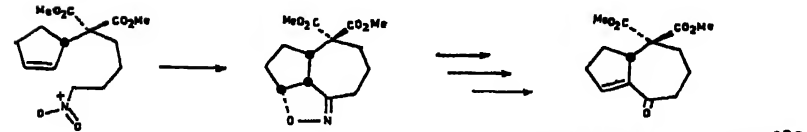


Chelidonine[104]

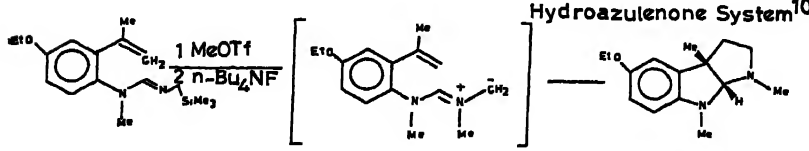
C-Aromatic taxane skeleton[105]



Campherenone[99]



Hydroazulenone System[100]



Eserethole

readily assembled. A wide variety of suitable substrates has enabled the syntheses of various alkaloids, steroids, terpenoids and polycyclic hydrocarbons using this reaction. Closely related to the intramolecular Diels-Alder reaction are the intramolecular dipolar additions of 2-oxyallyl-iron(II)[99], species, nitrile oxides,[100] nitrones[101] and formamidineylides.[102]

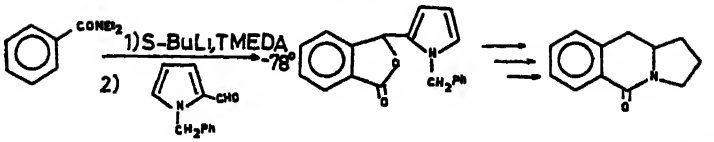
In illustrating applications of these reactions to organic synthesis, some representative examples are shown in the Scheme 18.[99–105]

Directed Metallations

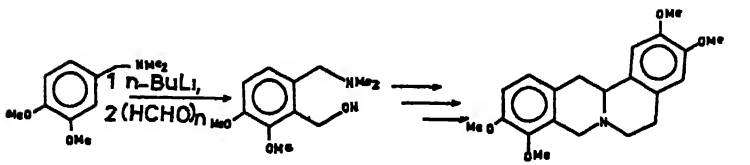
The commercial availability of strong bases like the akyllithiums and lithium dialkylamides has revolutionized the practice of organic synthesis. It has now become possible to generate carbanions quantitatively from very weakly acidic compounds with good selectivity. Aromatic systems can be readily metallated, especially with alkyllithiums. The ease and selectivity of metallation is governed to a large extent by the choice of substitutents; thus groups like methoxy, methoxymethyl, secondary and tertiary amides, oxazolines, secondary and tertiary sulfonamides are among the many substituents which direct the metallation to an *ortho* substituted product.[106] Such a process is of great synthetic utility as the common methods of introducing a substituent on to an aromatic ring are *via* an electrophilic substitution and the regiochemistry is governed largely by steric factors, making *ortho* substitution almost impossible or at best a minor pathway. Now, the heteroatom directed lithiation reaction is an important strategy and is extensively employed in organic synthesis. A few examples illustrating its use are given in Scheme 19.[107–109]

A second way of achieving directed metallation is via a metal-halogen exchange, the Grignard reaction being the best known example. Lithiations can be successfully realized using an alkyllithium as the metallating agent, and since a variety of halides can be easily prepared, this reaction offers considerable synthetic latitude. Synthesis of daunomycinone by Swenton[45] through the reaction between a lithiated bisketal of a quione with 3-methoxyphthalic anhydride is one of the pleasing applications of this concept, Scheme 20.[45,110,111]

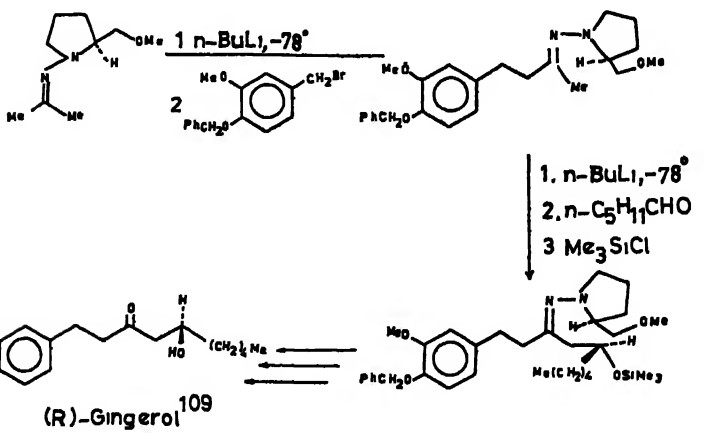
Scheme 19



ref.107



Tetrahydropalmatine[108]

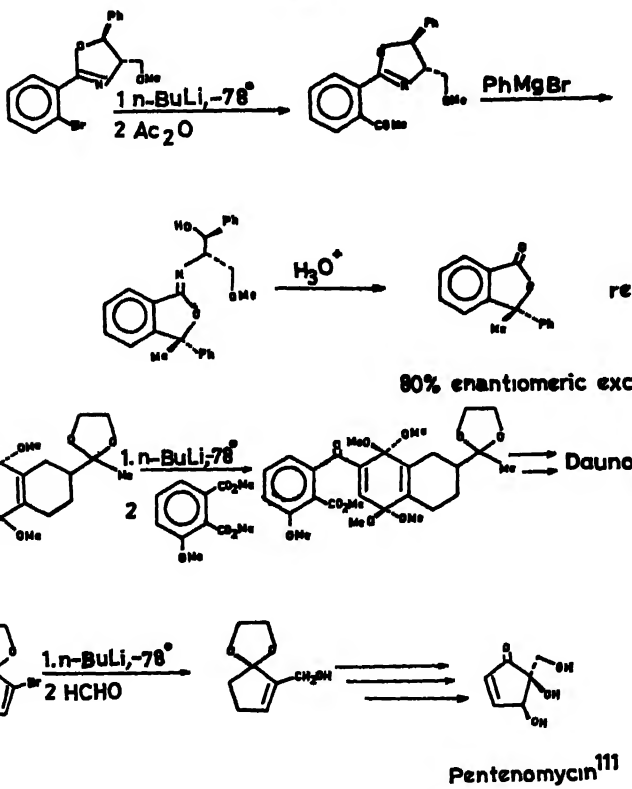


(R)-Gingerol[109]

Directed metallation can also be achieved by a transmetallation reaction The most common reactions of this type are exchanges of lithium for tin, selenium or silicon. While the reaction of lithium-silicon exchange has been known for a long time and applied for the regiospecific synthesis of lithium enolates,[113] the other two exchange reactions are of more recent vintage. As many tin and silicon compounds are readily available and the metallation can also be easily accomplished, a variety of interesting transformations can be brought about, some of which are shown in Scheme 21.[113–115]

Directed metallation can also be used for asymmetric synthesis, especially enantioselective alkylations of ketones as shown in Schemes 19 and 20. Although the metallations discussed so far have been exclusively lithiations, directed metallations are possible with other metals as well, of which palladium is the most important, Scheme 22.[116,117]

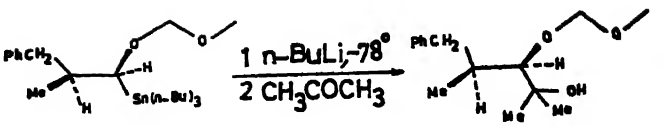
Scheme 20



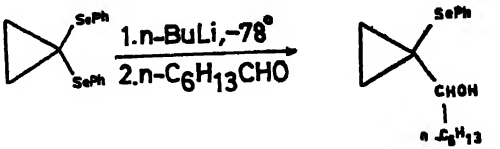
Acyclic Stereoselection

Carbon-carbon bond formation plays a cardinal role in OS. Of the many reactions which are available for this purpose, perhaps one of the most widely used is the aldol condensation. In its most general form, the reaction involves the attack of a carbon enolate

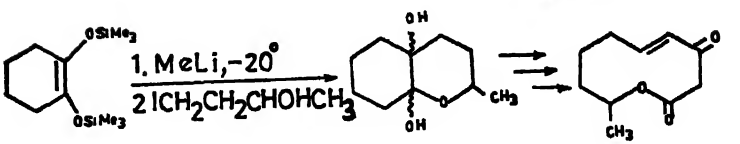
Scheme 21



ref.113

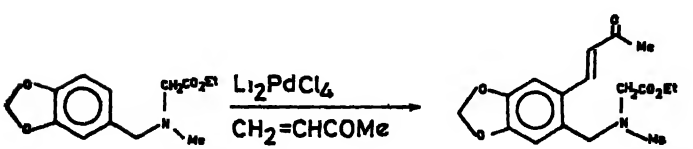


ref.114

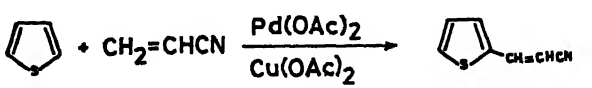


(±)-Diploidialide[115]

Scheme 22



ref 116



ref.117

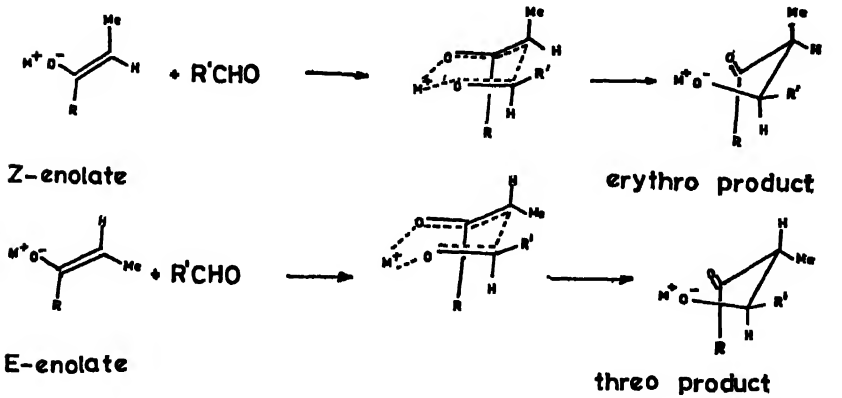
on a carbonyl carbon, leading to the generation of a β-hydroxy-carbonyl compound. If substituted precursors are employed, simultaneous to the formation of the carbon-carbon bond, two asymmetric centres are also created.

In the past decade or so, the isolation of complex natural products like ionophore and macrolide antibiotics, with their bewildering stereochemistry, has led to renewed interest in the

stereochemistry of the aldol reaction as a method for setting up the chirality present in such molecules. This naturally involves not only a selection between erythro and threo products (diastereoselection). but also between two erythro diastereomers (enantioselection). In the following paragraph, the approaches to diastereoselective and enantio-selective processes are discussed.

Conceptually, using a chair transition state as a reaction model, it is seen from Scheme 23 that a Z-enolate will give a product of erythro configuration. Similarly, an E-enolate will lead to a product with a threo configuration.

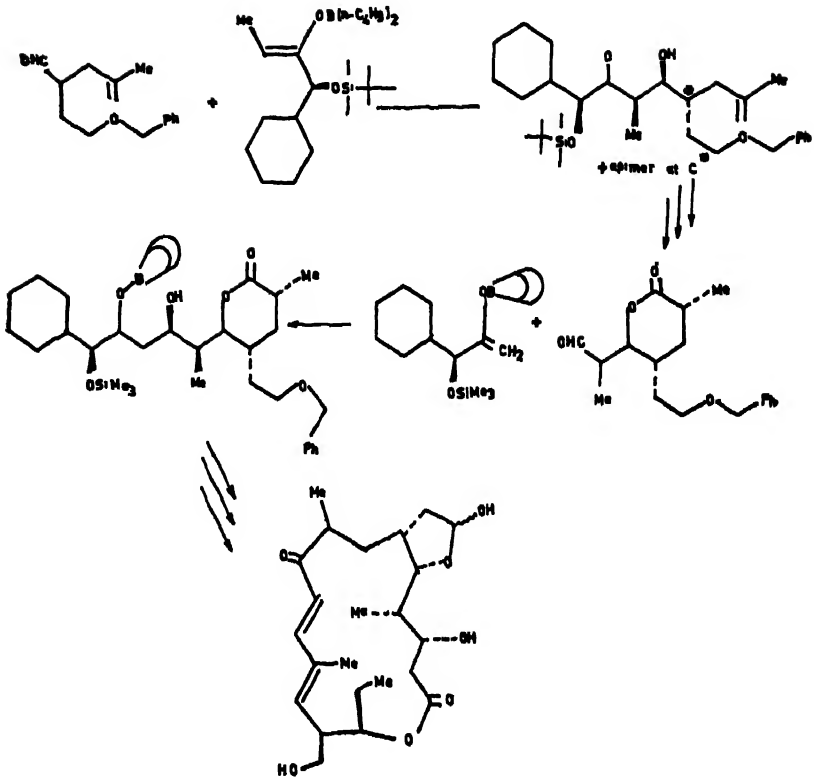
Scheme 23



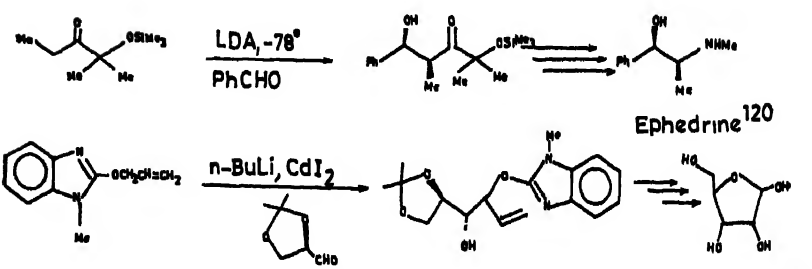
Thus, in order to ensure diasteroselectivity (predominance of erythro or threo product), the stereochemistry of reacting enolate should be Z or E, respectively.[118] This has been achieved in different ways *via* lithium, boron, zirconium and cadmium enolates as shown in the examples in Scheme 24.[119–121]

The realisation of enantioselectivity is a more difficult proposition. In an ingenious solution to this problem, Heathcock has developed a method called double stereodifferentiation, wherein the enantioselective bias of the enolate is reinforced by that of the carbonyl compound *via* the application of Cram's rule.[118] Enantioselective aldol condensations have also been realized by using a chiral enolate which is sterically demanding enough to provide the necessary chiral bias. Such approaches have been worked out by Still,[122]

Scheme 24



Tylonolide, the aglycone of Tylosin[119]



Ephedrine[120]

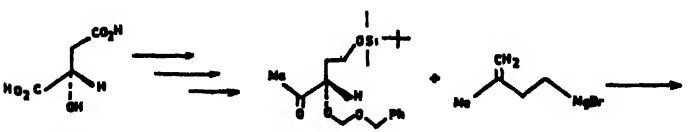
D-Ribose[121]

Masamune[120] and Evans,[123] and applied to natural product syntheses as illustrated in Scheme 25.

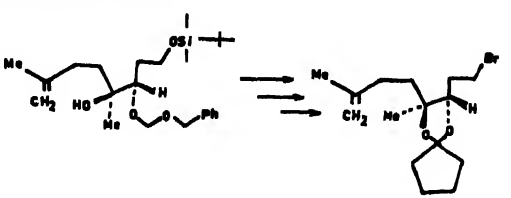
Carbohydrates as Chiral Synthons

One of the chief concerns in organic synthesis is the creation of chiral centres having the right absolute stereochemistry. In the earlier, more classical approaches, the standard technique was to effect a resolution on the racemic mixture and separate the enantiomers using a diastereomeric relationship. Such a process, however, is a wasteful one, as half the material is of the wrong stereochemistry and all the effort put into its synthesis comes to nought. Therefore, in recent years, increasing attention is being paid to effect 'asymmetric synthesis' without any resolutions, by employing a chiral starting material, reagent or catalyst.[124] Of these, the choice of a chiral precursor is an attractive one, especially as Nature is very generous in providing us with a host of chiral, naturally occurring compounds such as carbohydrates, terpenoids, steroids, amino acids and the like.

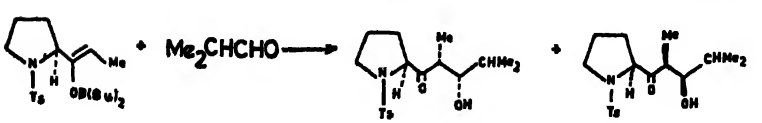
Scheme 25



(S)-(-) Malic acid



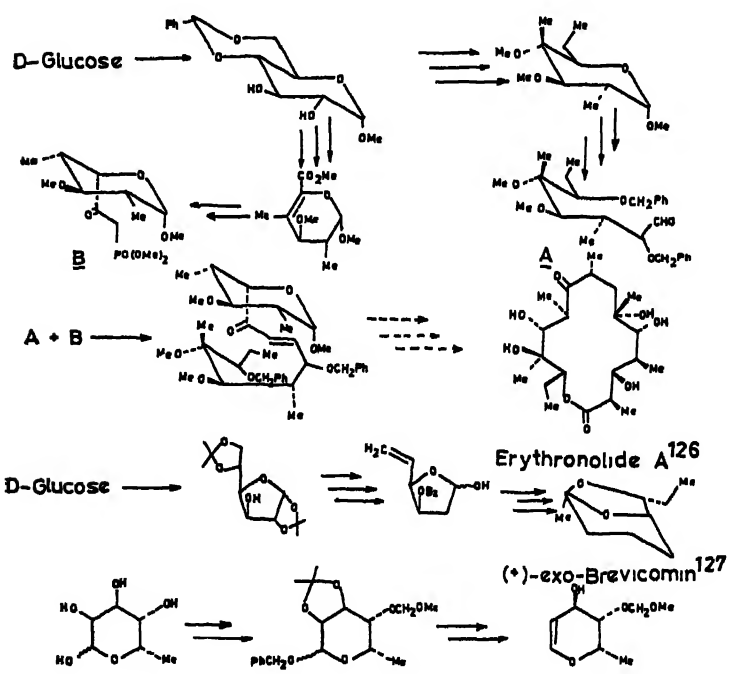
Monensin (7) Synthesis intermediate[122]



97 : 3 ref. 123.

Although syntheses have been devised using all of the above, carbohydrates as chiral precursors offer substantial advantages. For example, they are easily available at a very reasonable cost, have high stereochemical integrity and density of chiral centres, adopt conformations which are well studied and understood and finally are amenable to considerable functional group manipulation.[125] Numerous syntheses have been devised from carbohydrates as starting materials and some examples are included in Scheme 26.[16,126,127]

Scheme 26



Photochemical Reactions

Our knowledge of the interaction of light (UV and visible) with organic molecules has increased tremendously in the past two decades and with it our ability to use photochemistry for organic synthesis.

Photochemical reactions have many advantages They can be carried out at room temperatures or even below, show good stereo–, regio– and chemoselectivity and generally are 'clean' reactions. The commercial availability of preparative photochemical reactors makes it possible to carry out large scale runs efficiently.

From a preparative view point in organic synthesis, the most important photochemical reactions are the (2+2) cycloaddition of olefins,[128] meta cycloaddition of alkenes to aromatic compounds,[129] heteroatom directed photocylisations[130] and the various di-π-methane rearrangements.[131] The de Mayo reaction employs as its key step an olefinic (2+2) cycloaddition and has been used extensively in the synthesis of natural products.[128] Several interesting photochemical transformations are depicted in Scheme 27. It is worth pointing out that in many instances, photochemical reactions offer the easiest if not the only way to synthesize many strained and exotic molecules, exemplified by tetra-t-butyl-tetrahedrane (74)[54] and dodecahedrane (1).[3]

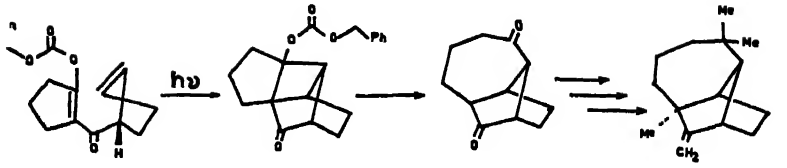
Organometallics in Organic Synthesis

Perhaps the most spectacular development in organic synthesis in the past decade is the extensive use of organometallic reagents to carry out with relative ease transformation almost impossible to achieve otherwise. Originally of interest in mechanistic studies and in physical organic chemistry, organometallics have now established themselves as synthetic reagents of unsurpassed utility.

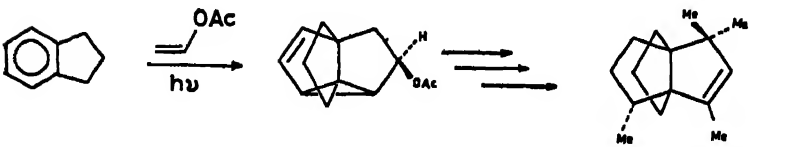
Although organometallic reagents involving main group elements like lithium, magnesium, aluminium, zinc, cadmium, mercury and tin have been in vogue for a long time, the main advance in recent years has come from the transition metal based reagents, especially those containing titanium, iron, chromium, cobalt, nickel, copper and palladium.[92] The ability of the metal fragment in stabilizing both cationic and anionic organic ligands attached to it is largely responsible for the versatility of these organometallic reagents. Thus, for example, π-allyl complexes of palladium react readily with nucleophiles while some allyl compounds of iron react well with electrophiles. The aromatic ring, normally resistant to nucleophilic substituion, undergoes facile reaction with various nucleophiles when complexed with a chromium tricarbonyl fragment.[92]

In a series of exhaustive experiments, Vollhardt[132] and Pauson[134]

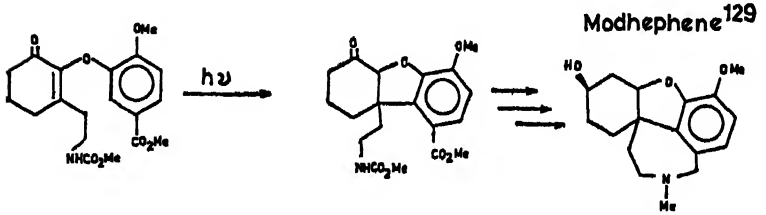
Scheme 27



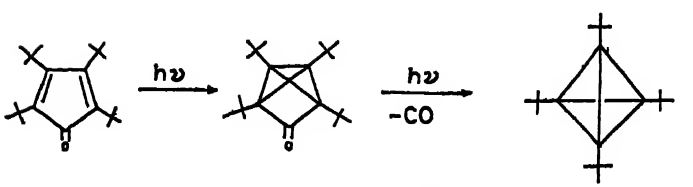
(+)Longifolene[132]



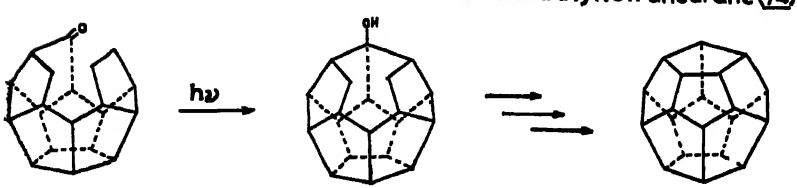
Modhephene[129]



Lycoramine[130]

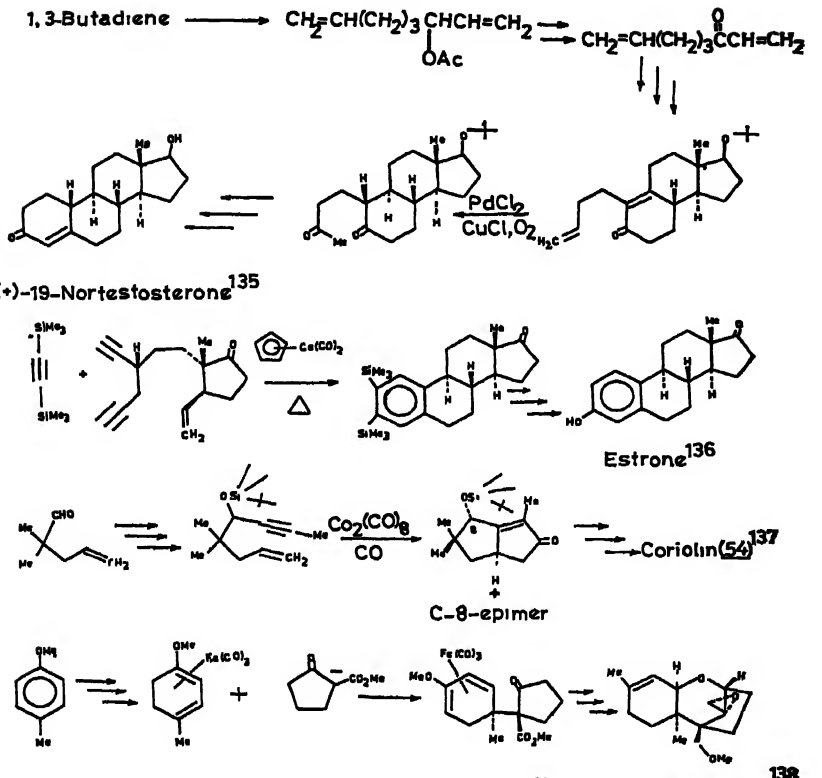


Tetra-t-butyltetrahedrane (74)[54]



Dodecahedrane (1)[3]

Scheme 28


1,3-Butadiene
PdCl2
CuCl,O2
(+)-19-Nortestosterone135
Estrone136
Co2(CO)8
CO
C-8-epimer
Coriolin(54)137
Verrucarin intermediate138
Cr(CO)6
LDA,-78°
CF3SO3H, then
NH4OH
Acoronone-B139

have shown the ability of some cobalt complexes to bring about cyclotrimerizations and cycloadditions, respectively. The chemistry of organocuprates is so well established today that it hardly needs any special mention. Scheme 28 highlights some of the unique transformations brought about by organometallic reagents.[135–139]

Thermal Pericyclic Reactions

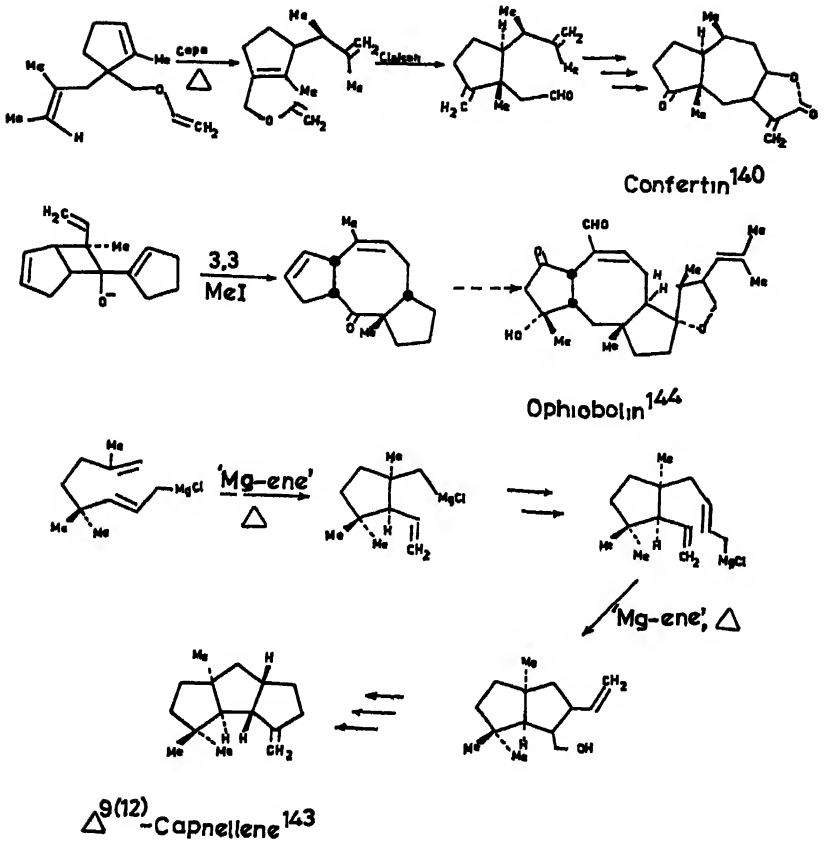
A variety of chemical reactions proceed through what can be termed as 'thermal processes'. Some of them are the well known Diels-Alder reaction, the Claisen rearrangement, the Cope rearrangement, the ene reaction and the electrocyclic reactions of conjugated olefins. While all the above mentioned reactions are well known and have been in practice for a long time, modifications and improvements are continuosly being made so as to improve their versatility. The intramolecular version of the Diels-Alder reaction is one such modification and has been considered in detail earlier because of its importance and popularity. Other useful variants include the tandem Cope-Claisen reaction[140] in which an unfavourable Cope rearrangement product serves as the precursor for a Claisen rearrangement thereby rendering the process irreversible; the anionic oxy-Cope rearrangement wherein a tremendous rate acceleration results on converting the precursor alcohol to an alkali metal alkoxide, preferably that of potassium[141] and the metallo-ene reaction[142,143] in which a metal atom (magnesium) undergoes migration instead of a hydrogen as is usual in an ene reaction, Scheme 29.[140,143,144]

The total synthesis of the highly symmetric superphane molecule[59] involves a sequence of thermal cyclisation reactions to form the binding ethylene units, Scheme 30. An elegant example of the use of thermal electrocyclic reactions is the total synthesis of novel natural products, endiandric acids by Nicolaou[145] Thus, the tetracyclic framework of endiandric acid A is generated in a single step with complete stereoselectivity at 8 chiral centres. Such is the power of thermal, orbital symmetry controlled electro-cyclizations when applied with ingenuity, Scheme 30.

Reagent Design

As pointed out earlier, development of new reagents is an integral part of organic synthesis. Here, in the last section on synthetic methodology, we focus attention on some general concepts

Scheme 29

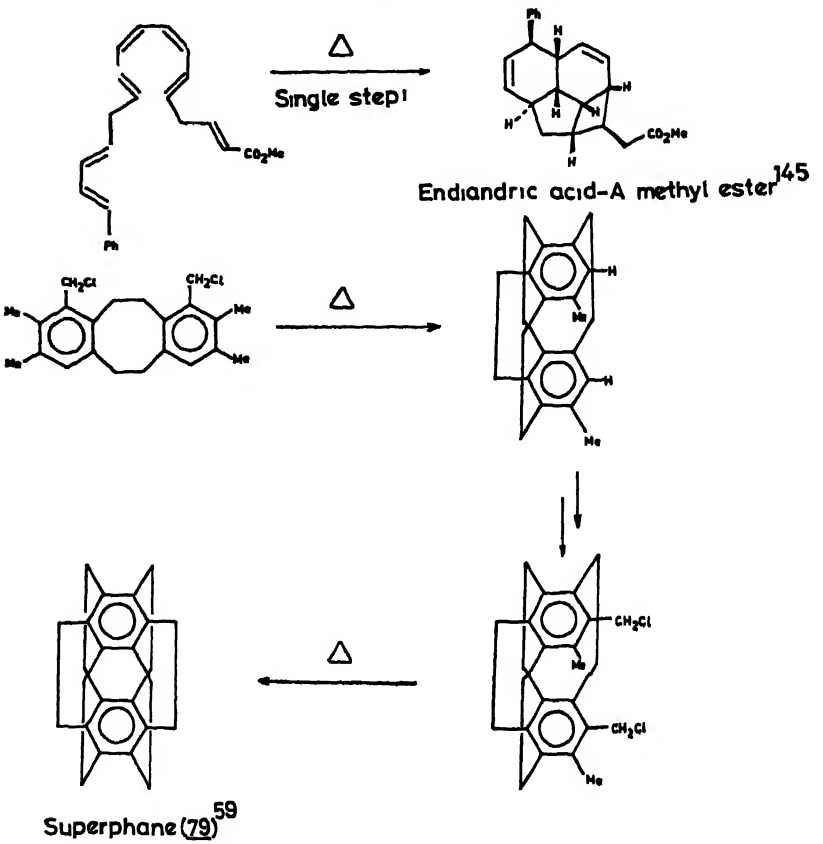


which have wide applicability in organic synthesis and have served to systematize existing knowledge and to spur the quest for new reactions and reagents. Under this heading of reagent design, four main concepts will be dealt with: (i) functional group equivalents (including those based on umpolung or reversed polarity);[146] (ii) protecting groups;[147] (iii) phase transfer reactions[148] and (iv) asymmetric synthesis.[124]

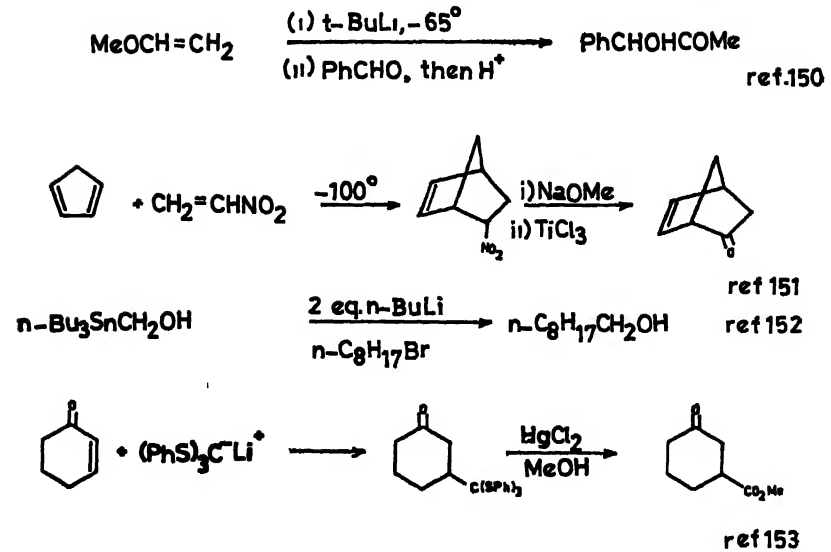
(i) The concept of functional group equivalents has been in use for a long time. A simple example is the classical Gabriel reaction, in which the phthalimide anion functions as an equivalent of

the amide anion. Similarly, the reactions of an alkyl halide with a nucleophile and of the Grignard reagent derived from the same halide with an electrophile serve to illustrate the electrophilic and nucleophilic character of the same alkyl group, respectively, thus underlying the importance of the umpolung concept. The systemization of such ideas into a general concept is largely due to the pioneering work of Corey and Seebach[149] on the chemistry of 1,3-dithiane and its derivatives. Today, numerous examples are available as functional group and umpolung equivalents for a wide variety of transformations and some of them are shown in Scheme 31.[150–158]

Scheme 30



Scheme 31



These equivalents play a significant role in organic synthesis as they make possible the successful execution of reactions which would not be feasible under normal circumstances due to incompatibility of reaction conditions and reagents.

(ii) Organic synthesis today deals mainly with polyfunctional molecules and any attempts at their total syntheses must be planned in such a manner that the most compatible functional group present in the molecule (to subsequent transformation) is introduced first and the least compatible last. Although such a logical sequence of reactions is the ideal approach, it is not always realisable in practice. As a consequence, functional groups likely to be affected by a particular reaction need to be 'protected' during that reaction and then 'deprotected' after the reaction. The recognition of such a need has resulted in the development of an extensive range of protecting groups for different functional groups, each of them differing in their ease of introduction and removal, as well as the degree of protection offered. An exhaustive survey of this rapidly growing area is outside the scope of this article as even monographs are available on the subject.[147]

(iii) The main difficulty in the use of inorganic reagents in organic synthesis is the insolubility of many of them in organic solvents and that of the organic substrates in water. One method of overcoming this difficulty is the use of polar aprotic solvents like dimethyl sulfoxide, dimethylformamide, acetonitrile and hexamethylphosphoramide A second technique is to use a phase transfer catalyst (PTC), which has the capacity to 'transfer' the inorganic reagent from the aqueous phase to the organic phase. Thus, it is now possible to dissolve potassium permanganate in benzene or sodium hydroxide in chloroform and many reactions which could once be carried out only in non-aqueous media can now be readily performed in water, thanks to PTC.

Two types of phase transfer catalysts are avilable. Crown ethers,[9] cryptands[62] and their derivatives belong to one category and their mode of action is by complexation of the metal ion by the crown ether and then its transfer to the organic phase as a hydrophobic aggregate. Thus, due to the break up of solvation in the aqueous phase and formation of ion pairs in the organic phase, the reagent is transferred to the organic phase. The second variety of phase transfer catalysts are mainly quaternary ammonium and phosphonium salts containing long chain aliphatic groups and occasionally aromatic rings as well.[145] These compounds have a hydrophilic 'head' and a hydrophobic 'tail' and therefore distribute themselves at the interface of the two phases and serve to bring together the inorganic reagent and the organic substrate to the interface where reaction can occur.

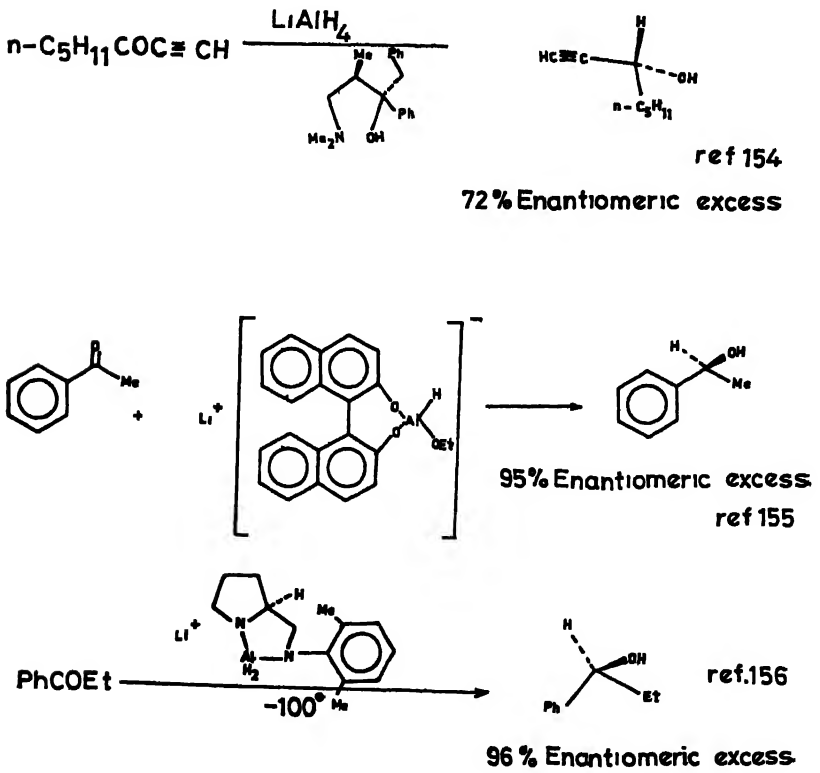
The main advantages of phase transfer catalysed reactions are the simiplicity and mildness of reaction conditions. A very wide variety of organic reactions are amenable to phase transfer catalysis and the list is growing almost every day. Although crown ethers and cryptands are fairly expensive reagents, truly catalytic quantities are sufficient. The quaternary ammonium salts, on the other hand, are quite inexpensive and readily available and should find wide application in industrial processes.

(iv) Asymmetric synthesis, or the preparation of optically active compounds directly without recourse to resolution of a racemic intermediate is one of the fast developing areas in organic synthesis. Certain aspects of asymmetric synthesis (eg. use of carbohydrates as chiral precursors and lithiation of optically active compounds) have been dealt with earlier. In this section, some other features of

asymmetric synthesis will be discussed. These can be broadly classified as asymmetric reductions, asymmetric epoxidations and asymmetric additions.

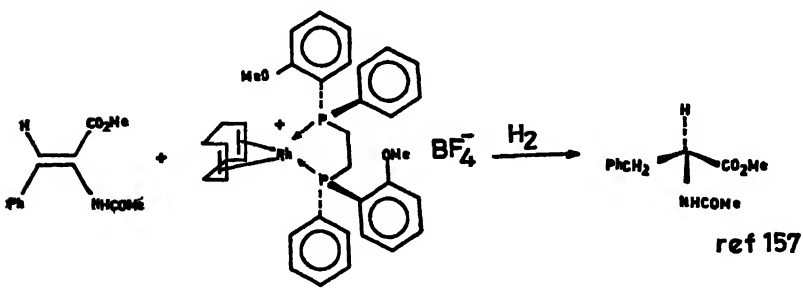
The reduction of unsymmetrical ketones to chiral secondary alcohols is a process which has been extensively studied. A fairly general method consists in modifying lithium aluminium hydride to a chiral reducing agent by complexation with different optically active ligands and some typical examples[154–156] are given in Scheme 32.

Scheme 32



Very closely related to the carbonyl group reduction is the asymmetric reduction of trisubstituted carbon-carbon double bonds. Such a reaction is of great interest as it can be used to synthesize chiral amino acids of either configuration, using a single olefinic precursor. Rhodium catalysts containing optically active phosphine ligands are very efficient in this type of a hydrogenation and the enantioselectivity is very high. As the catalyst can be recovered and reused, a small quantity of the catalyst is sufficient. Enantiomeric selectivity is controlled by the chirality of the ligand.[157] A process for the commercial manufacture of L-dopa (a drug for treatment of Parkinson's disease) using this method has been developed, Scheme 33.

Scheme 33

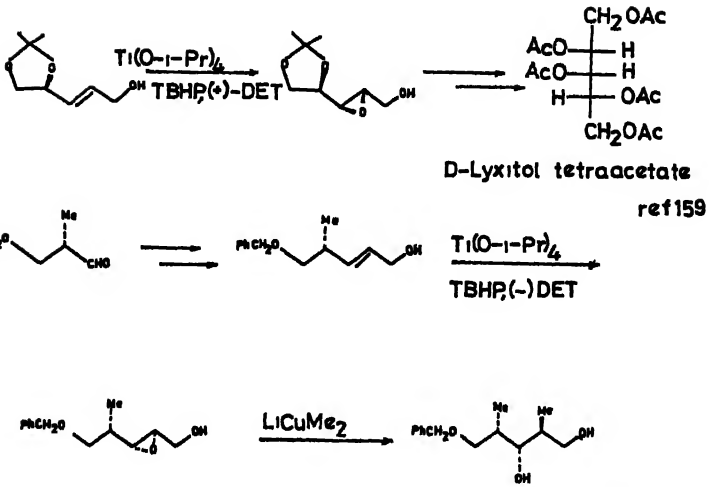


ref 157

An asymmetric epoxidation of tremendous potential was recently discovered by Sharpless.[158] Treatment of an allylic alcohol with a reagent mixture containing t-butylhydroperoxide, titanium tetraisopropoxide and diethyl tartarate leads to the formation of an epoxy alcohol whose configuration is dependent on the chirality of the tartarate ester used. The selectivities are better than 95 per cent or the asymmetric bias is > 19:1. As all the reagents are readily available and inexpensive, this method is an important advance in asymmetric synthesis and has been used in the synthesis of rifamycin S[28] and of all possible pentoses and hexoses.[159] Some examples are given in Scheme 34.

The introduction of a substituent with chirality at the α-position of an aldehyde or carboxylic acid is a very useful process. Three methods are available to do this and all of them use a chiral heterocycle as a template to provide the necessary asymmetric bias to the

Scheme 34



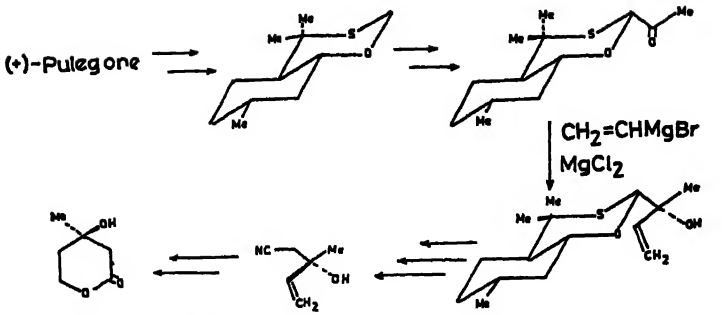
Rifamycin-S Synthesis intermediate[28]

reaction, usually involving addition of nucleophile. The heterocyclic template is then removed and recovered, so that it can be reused. Thus Meyers,[110] Eliel[160] and Mukaiyama[156] have employed an oxazoline, an oxathiane and a pyrrolidine as the asymmetric heterocyclic template, respectively. The use of this methodology in asymmetric synthesis is exemplified in Scheme 35.

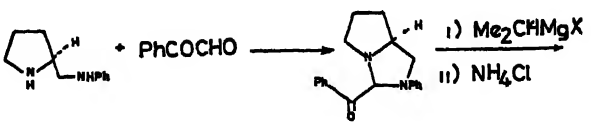
4. The Indian Scene

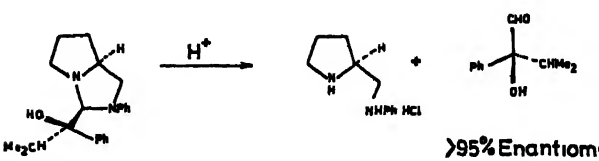
Synthetic organic chemistry has been practised in India as a serious scientific endeavour for over half a century. Inspite of this long period of activity and the fact that organic chemists enjoy numerical superiority among the scientists in India there is very little synthetic chemistry of international standards being done here at the moment. The memories of some worthwhile synthetic chemistry done in our country in the 1930-60 period in the area of naturally occurring coloring matters, synthetic dyes, steroids and terpenes have already faded. The 1960-80 interregnum was by and large a disappointing period for synthetic organic chemistry and barring a few exceptional efforts in terpene and alkaloid synthesis, most of the work emanating from our laboratories was directed towards making more and more

Scheme 35



R-(+)-Mevalolactone[160]





>95% Enantiomeric excess[156]

compounds without any new idea or novelty behind them. This was the time when synthetic organic chemistry was beginning to make big strides all over the world and we seemed to have missed the bus. Our bleak portrayal of the state of organic synthesis in India is based on our incisive analysis and is supported by considerable data that we have collected. It should suffice here to quote the citations mentioned from work done in India, by Fieser and Fieser,[93] a work universally used and referred to by synthetic organic chemists. On scanning nearly 20,000 references cited in the 10 volumes (1967-82) of Fieser and Fieser, we found that contributions from India accounted for less than 0.5 percent. The trend is quite unmistakable, even after granting that the compilation by Fieser and Fieser may not be wholly objective.

However, there is a silver lining in this dismal scenario. In the past 2 years or so, synthetic activity in several laboratories across the country has shown signs of recovery. Synthetic projects aimed at the total synthesis of complex polycyclic terpenoids, steroids, anthracyclines, pheromones, polypeptides, platonic hydrocarbons and development of new reagents are being energetically pursued. A few of these are clearly state-of-the-art efforts. It is our sincere hope that this perspective will inspire at least a few organic chemists to undertake work on more challenging and purposeful synthetic objectives.

5. Conclusion

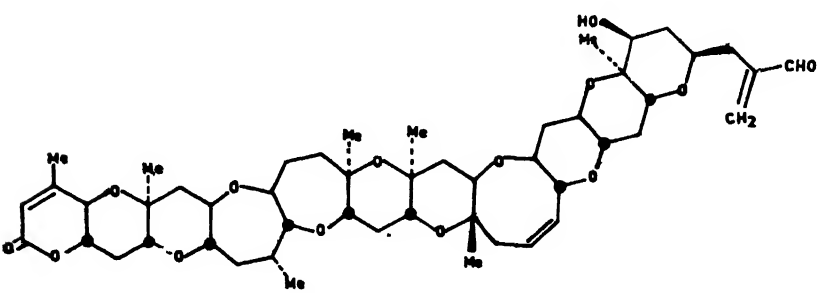
In the foregoing narration, we have tried to illuminate how the challenges posed by the 'diabolic concatenation of reactive groupings', the 'plethora of asymmetric centres', the 'repetitious monstrosities' and the 'very fugitive'[161] have been convincingly met. Indeed, developments in organic synthesis in the past few decades have been truly spectacular. So far so good, but, what about the future? Which way would OS continue its triumphant march? It is not possible to answer these questions with complete precision but one can expect future developments on the basis of certain trends that are already emerging.

To begin with, there is little doubt that for the purist, the artist, the prime motivation for synthesis will be the intellectual challenge and urge to create complex molecular arrays. As Nature continues to unravel her inexhaustible repertory, in the form of novel structures from hitherto unexplored sources like marine, insect and animal worlds, new synthetic targets will continue to emerge (e.g., *86*)[162] and we will witness more and more total syntheses on a grand scale. It may be added here that increasing applications of methods of artificial intelligence[163] in analysing synthetic problems will complement the mind's efforts in the planning and execution of synthetic ventures.

There have been some startling discoveries in the field of molecular biology in the past few decades. These developments have influenced the thinking of synthetic organic chemists in a significant way. As a result, efforts have been directed both towards the synthesis of biopolymers particularly proteins, nucleotides, hormones, etc. and towords simulating their biological functions with synthetic analogues. It is this latter area that is going to engage a great deal

of attention in coming years. Synthetic chemists will have to address themselves to the task of designing compounds which would not only exhibit the selectivity, efficiency and speed of enzymes but whose reactions could be carried out at ambient temperatures and in aqueous media. Mounting energy costs and depleting fossil fuel reserves only underscore the need for greater thrust in this area. We believe study of organic reactions on solid matrix through immobilized reagents and in aqueous media using micellar aggregates will become increasingly popular.

Finally, synthetic studies on consumer products like pharmaceuticals, fine chemicals, flavours and pesticides will continue to receive attention, particularly in developing countries, as cheaper and efficient methods of synthesis are sought. In this regard, more and more use of renewable, abundantly available natural products as synthons (e.g. conversion of Δ^3-carene to menthol and pyrethroids)[164] and chemicoenzymatic approach to synthesis (possible conversion of penicillins to thienamycins and cephalosphorins)[165] will be pursued.



Brevetoxin B (86)[162]

6. References

1. Barton, D. H. R. and Ollis, W. D. (Eds.) (1979) *Comprehensive Organic Chemistry, Vols.* 1–6, Pergamon Press, Oxford.
2. (a) Fleming, I. (1973) *Selected Organic Syntheses*, John Wiley and Sons, London, (b) Ireland, R. E (1969) *Organic Synthesis*, Prentice Hall Inc. New Jersey; (c) Anand, N., Bindra, J S and Ranganathan, S. (1970) *Art in Organic Syntheses*, Holden-Day Inc., San Francisco; (d) Turner, S. (1976) *The Design of Organic Synthesis*, Elsevier, Amsterdam.
3. Paquette, L. A , Teransky, R. J., Balogh, D. W. and Kentgen, G. (1983) *J. Am. Chem.*, 105, 5446.
4. Woodward, R. B (1973) *Pure Appl. Chem.*, 33, 145.
5. Aoyagi, Y., Katano, K., Suguna, H , Primeau, J., Chang, L. H. and Hecht, S. M. (1982) *J. Am. Chem. Soc.*, 104, 5537; Takita, T., Umezawa, Y., Saito, S., Morishima, H., Naganawa, H., Umezawa, H., Tsuchiya, T., Miyake, T. Kageyama, S., Umezawa, S., Muraoka, Y., Suzuki, M., Otsuka, M. Narita, M., Kobayashi, S. and Ohno, M. (1982) *Tetrahedron Letts.*, 23, 521.
6. Still, W. C. and Ohmizu, H. (1981) *J. Org. Chem.*, 46, 5242, see also, Roush, W. and Blizzard, T. A. (1983) *ibid.*, 48, 758.
7. Girotra, N. N. and Wendler, N. L. (1982) *Tetrahedron Letts.*, 23, 5501; Grieco, P. A., Zelle, R. E., Lis, R. and Finn, J. (1980) *J. Am. Chem Soc.*, 105, 1403; Hsu, C. T., Wang, N. Y , Latimer, L. H. and Sih, C. J. (1983) *ibid.*, 105, 593.
8. Cha, J. K., Christ, W. J., Finan, J M., Fujioka, H , Kishi, Y., Klein, L. L. Ko, S. S., Leder, J., McWhorter, W. W. Jr., Pfaff, K. P., Yonaga, M. Uemura, D. and Hirata, Y. (1982) *J Am Chem. Soc.*, 104, 7369 and references cited therein.
9. Izatt, R. M. and Christensen, J. J. Eds. (1978) *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, New York.
10. Agtarap, A., Chamberlain, J. W., Pinkerton, M. and Steinrauf, L. (1967) *J. Am. Chem. Soc.*, 89, 5737.
11. Westley, J. W., Blount, J. F., Evans, R. H. Jr., Stempel, A. and Berger, J. (1974) *Antibiot J.*, 27, 597.
12. Westley, J. W., Evans, R. H., Liu, C. M., Hermann, T. E. and Blount, J. F. (1978) *J. Am. Chem. Soc.*, 100, 6784.
13. Cheny, M. O., Demarco, P. V., Jones, N. D., Jones and Occolowitz, J. L. (1974) *ibid.*, 96, 1932.
14. Heathcock, C. H., Pirrung, M. C., Buse, C. T., Hagen, J. P., Young, S. D. and Sohn, J. E. (1979) *ibid.*, 101, 7077.
15. (a) Evans, D. A., Nelson, J. V., Vogel, E. and Taber, T. R. (1981) *ibid.*, 103, 3099; (b) Masamune, S , Choy, W., Kerdesky, F. A. J. and Imperiali, B. (1981) *ibid* , 103, 1566.

16. Nakata, T., Schmid, G., Vranesik, B., Okigawa, M., Smith-Palmer, T. and Kishi, Y. (1978) *ibid.*, 100, 2933; (b) Ireland, R. E , Anderson, R. C. Badoud, R., Fitrzsimmons, B. J., MacGarvey, G. J., Thaisrivongs, S. and Wilcox, C. S. (1983) *ibid* , 105, 1988

17. (a) Nicolaou, K. C., Papahatjis, D P., Claremon, D. A. and Dolle, R. E. (1981) *ibid.*, 103, 6967, Nicolaou, K. C., Claremon, D. A., Papahatjis, D. P. and Magolda, R. L. (1981) *ibid.*, 103, 6969; (b) Edwards, M. P., Ley, S. V., Lister, S. G. and Palmer, B. D. (1983) *J. Chem. Soc. Chem. Comm.*, 630.

18. (a) Evans, D. A., Sacks, C. E., Kleschik, W. A. and Taber, T. R. (1979) *J Am Chem Soc* , 101, 6789; (b) Grieco, P. A., Williams, E., Tanaka, H. and Gilman, S. (1980) *J. Org. Chem.*, 45, 3537.

19. (a) Schmid, G , Fukuyama, T., Akasaka and Kishi, Y. (1979) *J Am. Chem.* Soc , 101, 259; Fukuyama, T., Wang, C-L. J. and Kishi, Y. (1979) *ibid* , 101, 260; Fukuyama. T., Akasaka. K., Karanewsky, D. S., Schmid, G. and Kishi, Y. (1979) *ibid* , 101, 262, (b) Collum, D. B., McDonald, J. H. and Still, W. C. (1980) *ibid* , 102, 2117, 2118, 2120.

20. Djerassi, C. and Zderic, J. A (1956) *ibid.*, 78, 6390; Rickards, R. W. and Smith, R. M. (1970) *Tetrahedron Letts* , 1025; Manwaring, D. G. Rickards, R. W and Smith, R. M. (1970) *ibid.*, 1029.

21. Wiley, P. F., Gerzon, K , Flynn, E. H., Sigal M V. Jr., Weaver, O. Quarck, U. C , Chauvette, R. R. and Manahan, R. (1957) *J. Am. Chem. Soc.*, 79, 6062; Harris, D. R., McGeachin, S. G. and Mills H. H. (1965), *Tetrahedron Letts* , 679

22. Prelog, V. (1963) *Pure appl. Chem.*, 7, 551; Rinehart, K. L. Jr. (1972) *Accts. Chem. Res* , 5, 57, Sensi P (1975) *Pure appl. Chem* , 41, 15.

23. Kupchan, S. M , Komoda, Y., Court, W. A., Thomas, G. J., Smith, R. M., Karim, A., Gilmore, C. J., Haltiwanger, R C. and Bryan, R. F. (1972) *J. Am. Chem. Soc.*, 94, 1354

24. Masamune, S., Kim, C. V., Wilson, K. E , Spessard, G. O., Georghiou, P. E. and Bates, G. S. (1975) *J. Am. Chem. Soc* , 97, 3512; Masamune, S., Yamamto. H , Kamata, S. and Fukuzawa. A. (1975) *ibid.*, 97, 3513.

25. Grieco, P. A., Ohfume, Y., Yokoyama, Y. and Owens, W. (1979) *ibid.*, 101. 4749. For another recent synthesis, see. Ireland, R. E., Daub, J. P., Mandel, G. S. and Mandel, N. S. (1983) *J Org. Chem.*, 48, 1312.

26. Woodward, R B. et al. (1981) *J. Am. Chem. Soc.*, 103, 3210, 3213, 3215

27. Stork, G., Paterson, I. and Lee, F. K. C. (1982) *ibid.*, 104, 4686; see also Corey, E J., Hopkins, P. B., Kim, S., Yoo, S., Nambiar, K. P. and Falck, J. R. (1979) 101, 7131.

28. Kishi, Y. (1981) *Pure appl. Chem.*, 53, 1163; Nagoaka, H. and Kishi, Y. (1981) *Tetrahedron*, 37, 3873.

29. Corey, E. J., Weigel, L. O, Chamberlin, A. R., Cho, H. and Hua, D. H. (1980) *J. Am. Chem. Sec.*, 102, 6615.

30. Meyers, A. I., Reider, P. J, Campbell, A. L (1980) *ibid.*, 102, 6597.

31. Isobe, M, Kitamura, M. and Goto, T. (1982) *ibid.*, 104, 4997.

32. Terahara, A., Haneishi, T. and Arai, M. (1979) *Heterocycles*, 13, 353 and references cited therein.

33. Martin, D. G., Slomp, G., Mizsak, S., Duchamp, D. J. and Chidester, C. G. (1970) *Tetrahedron Letts.*, 4901; Duchamp, D. J. and Chidester, C. G. (1972) *Acta Crystallogr. Sect. B.*, 28, 173.

34. Ranieri, R. L. and Calton, G. J. (1978) *Tetrahedron Letts*, 499.

35. Takahashi, S, Naganawa, H., Iinuma, H., Takita, T., Maeda, K. and Umezawa, H (1971) *Tetrahedron Letts*, 1955; Takita, T., Umezawa, H. Kunishima, M., Nakayama, Y. and Iitaka, Y. (1974) *Antibiots. J.*, 27, 301.

36. Zalkow, L H, Harris, R. N., Van Derveer, D. and Bertrand, J. A. (1977) *J. Chem. Soc., Chem. Comm.*, 456; Bohlmann, F, Le Van, N. and Pickardt J. (1977) *Chem. Ber.*, 110, 3777.

37. Zalkow, L. H, Harris, R. N. and Van Derveer, D. (1978) *J. Chem. Soc., Chem. Comm.*, 420.

38. Jomon, K., Kuroda, Y., Ajisaka, M. and Sakai, H. (1972) *Antibiots, J.*, 25, 271.

39. Corbett, R. E., Lauren, D. R. and Weavers, R. T. (1979) *J. Chem. Soc.*, Perkin Trans. I, 1774.

40. Little, R D., Muller, G. W., Venegas, M. G., Carroji, G. L., Bukhari, A. Patton, L. and Stone, K. (1981) *Tetrahedron*, 37, 4371.

41. Wender, P. A. and Dreyer, G. B. (1981), *ibid.*, 37, 4445.

42. Mehta, G, Srikrishna, A., Reddy, A. V. and Nair, M. S. (1981) *ibid.*, 37, 4543.

43. DiMarco, A., Gaetani, M., Orezzi, P., Scarpinato, B., Silvestrini, R., Soldati, M., Dasdia, T. and Valentini L. (1964) *Nature*, 201, 706.

44. Arcamone, F., Granceschi, G., Penco, S. and Selva, A. (1969) *Tetrahedron Letts.*, 1007.

45. Swenton, J. S. and Raynolds, P. W. (1978) *J. Am. Chem. Soc.*, 100, 6118.

46. Kelly, T. R., Vaya, J. and Ananthasubramanian, L. (1980) *J. Am. Chem. Soc.*, 102, 5984.

47. Gordon, J. J., Jackman, L. M., Ollis, W. D. and Sutherland, J. O. (1960) *Tetrahedron Letts.*, 28, Kumar, V., Remers, W. A. and Grulich, R. E. (1977) *Antibiot. J.*, 30.

48. Brazhnikova, M. G., Zbarsky, V. B., Ponomarkeno, V. I. and Potapova, N. P. (1974) *Antibiot. J.*, 27, 254; Wani, M. C. Taylor, H. L. Watt, M. E. McPhail, A. T. and Onan, K. D. (1975) *J. Am. Chem Soc.*, 97, 5955.

49. Wiley, P. F., Kelly, R. B., Caron, E. L., Wiley, V. H., Johnson, J. H. Mackellar, F., A. and Mizsak, S. A. (1977) *ibid.*, 99, 542, Arora, S. K. (1983) *ibid.*, 105, 1328.

50. Kerdesky, F. A. J. and Cava, M. P. (1978) *ibid.*, 100, 3635.

51. Rama Rao, A. V., Venkatswamy, G., Javeed, S. M.. Deshpande, V. J. and Rao, B. Ramamohan (1983) *J. Org. Chem.*, 48, 1552.

52 Mc Namara, J M. and Kishi, Y. (1982) *J. Am. Chem. Soc*, 104, 7371.

53. March, J. (1977) *Advanced Organic Chemistry*, Mc Graw Hill, New York.

54. Maier, G., Pfriem, S, Schafer, U. and Matusch, R. (1978) *Angew. Chem. Int. Ed. Engl.*, 17, 520.

55. Wiberg, K. B and Walker, F. H. (1982) *J. Am. Chem. Soc.*, 104, 5239.

56. Eaton, P. E., Orr, Y. S. and Branca, S. J. (1981) *ibid.*, 103, 2134.

57. Marshall, J. A. and Lewellyn, M (1977) *ibid.*, 99, 3508.

58. Eaton, P E., Muller, R. H., Carlson, G. R., Gullison, D. A., Cooper, G. F. Chou, T. C. and Kvebs, E. P. (1977) *ibid.*, 99, 2751.

59. Sekine, Y. and Boekelheide, V. (1981) *ibid*, 103, 1777.

60. Diederich, F. and Staab, H. A. (1978) *Angew. Chem. Int. Ed. Engl.*, 17, 372.

61. Martin, R. H, Marren, G. and Schurter, J. J. (1969), *Tetrahedron Letts.*, 3683.

62. Bender, M. L. and Komiyama, M. (1978) *Cyclodextrin Chemistry, Springer-Verlag*, Berlin.

63. Lehn, J M. (1978) *Accts. Chem. Res.*, 11, 49.

64. Cram, D. J., Kaneda, T., Helgeson, R. C. and Lein, G. M. (1979) *J. Am. Chem. Soc.*, 101, 6752.

65 Cram, D. J. and Katz, H. E. (1983). *ibid.*, 105, 135.

66. Cram, D. J. (1983) *Science*, 219, 1177.

67. Torrance, J. B. (1979) *Accts. Chem. Res.*, 12, 79.

68. Ferraris, J., Cowan, D. O., Walatka, V. Jr. and Perlstein, J. H. (1973) *J Am. Chem. Soc*, 95, 948.

69 Wegner, G. (1981) *Angew. Chem. Intt. Ed. Engl.*, 20, 311.

70. Scharf, H. D., Fleischhaver, J, Leismann, H., Ressler, I., Schlekcr, W. and Weitz, R. (1979) *Angew. Chem. Intl. Ed.*, 18, 652.

71. Maruyama, K., Terada, K. and Yamamoto, Y. (1981). *Chem. Letts.*, 839.

72. Mukai, T. and Yamashita, Y. (1978) *Tetrahedron Letts.*, 357.

73. Hamada, T., Iijima, H., Yamamoto, T., Numao, N., Hirao, K. and Yonemitsu, O. (1980) *J. Chem. Soc. Chem. Comm.*, 696.

74. Mehta, G. and Srikrishna, A. (1982) *ibid.*, 217.

75. Fleming, I., Iqbal, J. and Krebs, E. P. (1983) *Tetrahedron*, 39, 841.

76. Burford, C., Cooke, F., Roy, G. and Magnus, P. (1983) *ibid.*, 39, 867.

77 Utimoto, K., Wakabayashi, Y., Horiie, T., Inone, M , Shishiyama, Y. Obayashi, M. and Nazaki, H. (1983) *ibid.*, 39, 967.

78. Danishefsky, S., Kerwin, J. F. and Kobayshi, S. (1982) *J. Am. Chem. Soc.*, 104, 360.

79. Tsunoda, T., Suzuki, M. and Noyori, R. (1980) *Tetrahedron Letts*, 71.

80. Vickery, E. H., Pohler, L. F. and Eisenbraun, E. I (1979) *J. Org Chem.*, 44, 4444.

81. Trost, B. M. and Curran, D. P. (1980) *J. Am. Chem. Soc.*, 102, 5699.

82. Cowell, A. and Stille, J. K. (1980) *ibid.*, 102, 4193.

83. Trost, B. M Rungo, T. A. and Jungheim, L. N (1980) *ibid.*, 102, 2840

84. Godleski, S. A. Heacock, D. J. Meinhart J D. and Wallendael, S. V. (1983) *J. Org. Chem.*, 48, 2101.

85. Overman, L. E. and Renaldo, A. F. (1983) *Tetrahedron Lett.*, 24, 3757.

86. Ito, Y., Hirao, T. and Saegusa, T. (1978) *J. Org. Chem*, 43, 1011.

87. Hoye, T. R. and Caruso, A. J. (1981) *J. Org. Chem.*, 46, 1198.

88. Pitteloud, R. and Petrzilka, M. (1979) *Helv. Chim. Acta*, 62, 1319.

89. Yamakawa, K., Satoh, T., Ohbe, N., Sakaguchi, R., Takita, S. and Tamura, N. (1981) *Tetrahedron*, 37, 473.

90. Grieco, P. A., Jaw, J. Y. Claremon, D. A. and Nicolaou, K. C. (1981) *J. Org. Chem.*, 46, 1215.

91. Jackson, W. P , Ley, S. V and Whittle A J. (1980) *J. Chem. Soc. Chem. Comm*, 1173.

92. Wilkinson, G., Stone, F. G. A. and Abel, E W. (Eds.), (1982) *Comprehensive Organometallic Chemistry*, Pergamon Press, Oxford.

93. Fieser, L. F. and Fieser, M. Reagents in Organic Synthesis, Vols. 1-10, Wiley-Interscience, New York.

94. Blickenstaff, R. T., Ghosh, A. C. and Wolf, G. C. (1974)] *Total Synthesis of Steroids*, Academic Press, New York; Akhrem, A. A. and Titav Y, A. (1970) *Total Steroid Synthesis*, Plenum Press, New York.

95. Kametani, T and Nemata, H. (1981) *Tetrahedron*, 37, 3.

96. Johnson, W. S. (1976) *Biorg. Chem*, 5, 51.

97. Posner, G. H., Mallamo, J. P. and Black, A. Y. (1981) *Tetrahedron*, 37, 3921.

98. Brieger, G. and Bennett, J N. (1980) *Chem. Rev.*, 80, 63. Oppolzer, W. (1977) *Angew. Chem. Intl Ed. Engl.*, 16, 10; Mehta, G. (1976) *J. Chem. Educ*, 53, 551.

99. Noyori, R., Nishizawa, M., Shimizu, F., Haryakawa, Y., Maryoka, K., Hashimoto, S., Yamamoto, H. and Nozaki, H. (1979) *J. Am. Chem, Soc.*, 101, 220

100. Kozikowski, A. P, Mugrage, B. B., Wang, B C. and Xu, Z. (1983) *Tetrahedron Letts.*, 3705.

101. Tufariello, J. J. (1979) *Acc Chem. Res.*, 12, 396; Confalone, P. N. and Huie, E. M. (1983) *J. Org Chem.*, 48, 2995 and references cited therein.

102. Smith, R. and Livinghouse, T. (1983) *ibid.*, 48, 1554

103. Gallagher, T. and Magnus, P. (1983) *J. Am. Chem. Soc*, 105, 2086.

104. Oppolzer, W. and Keller, K. (1971) *ibid.*, 93, 3836.

105. Shea, K. J. and Davis, P D. (1983) *Angew. Chem. Intl. Ed. Eng.*, 22, 419.

106. Parham, W. E and Bradsher, C. K. (1982) *Accts. Chem. Res.*, 15, 300; Beak, P. and Snieckus, V. (1982) *Accts Chem. Res.*, 15, 306; Newkome G. R. Ed. (1983) *Heteroatom Directed Metallation in Heterocyclic Synthesis, Tetrahedron*, 39, 1955-2092.

107. Iwao, M, Mahalanbais, K. K., Watanabe, M., de Silva, S. O. and Snieckus, V. (1983) *ibid.*, 39, 1955.

108. Narasimhan, N. S., Mali R. S. and Kulkarni, B. K. (1983) *ibid.*, 39, 1975.

109. Enders, D, Eichenaner, H. and Pieter, R. (1979) *Chem. Ber.*, 112, 3703.

110. Meyers, A I, Hanagan, M. A., Trefonas, L. M. and Baker, R. J. (1983) *Tetrahedron*, 39, 1991.

111. Branca, S. J and Smith, A. B. (1978) *J. Am. Chem. Soc.*, 100, 7767.

112. House, H. O. (1972) *Modern Synthetic Reactions*, Benjamin, W. A. Menlo Park.

113. Still, W. C. and Sreekumar, C. (1980) *J. Am. Chem. Soc.*, 102, 1201.

114. Halazy, S, Lucchetti, J. and Krief, A. (1978) *Tetrahedron Lett.*, 3971.

115. Wakamatsu, T., Akasaka, K. and Ban, Y. (1979) *J. Org. Chem.*, 44, 2008.

116. Barr, N., Dyke, S. F. and Quessy, S. N. (1983) *J. Organometallic Chem.*, 253.

117. Maruyama, O., Yoshidomi, M., Fujiwara, Y. and Taniguchi, H. (1979) *Chem. Lett.*, 1229.

118. Heathcock, C. H. (1981) *Science*, 214, 395; Evans, D. A. (1981) *Pure and Appl. Chem*, 53, 1109.

119. Masamune, S., Lu, L. D. L. Jackson, W. P., Kaiho, T. and Toyoda, T. (1982) *J. Am. Chem. Soc.*, 104, 5523.

120. Heathcock, C. H., Buse, C. T., Kleschick, W. A., Pirrung, M. C., Sohn, J. E. and Lampe, J. (1980) *J Org Chem.*, 45, 1066.

121. Yamaguchi, M. and Mukaiyama, T. (1981) *Chem. Lett.*, 1005.

122. Collum, D. B., McDonald, J. H., III, and Still, W. C (1980) *J. Am. Chem. Soc*, 102, 2118.

123. Evans, D. A. and Taber, T. R. (1980) *Tetrahedron Lett.*, 21, 4675.

124. Mosher, H S. and Morrison, J. D. (1983) *Science*, 221, 1013.

125. Hanessian, S (1979) *Accts. Chem. Res*, 12, 159, Fraser-Reid, B. in Herz, W, Grisebach, H. and Kirby, G. W. Eds. (1980) *Progress in the Chemistry of Organic Natural Products*, Springer Verlag, Vienna, 39, 1.

126. Hanessian, S., Rancourt, G. and Guindon, Y. (1978) *Can. J. Chem.*, 56, 1843.

127. Sherk, A. E and Fraser-Reid, B. (1982) *J Org Chem.*, 47, 432.

128. Oppolzer, W. (1982) *Accts. Chem. Res*, 15, 135.

129. Wender, P. A. and Dreyer, G. B. (1982). *J. Am. Chem. Soc.*, 104, 5805.

130. Schultz, A. G., Yu, Y. K. and Berger, M. H. (1977) *ibid.*, 99, 8065.

131. Houk, K. N (1976) *Chem Rev.*, 76. 1. Hixson, S. S. Mariano, P. S. and Zimmerman, H. E. (1973) *ibid.*, 73, 531

132. Oppolzer, W. and Godel, T. (1978) *J. Am. Chem. Soc.*, 100, 2583.

133. Vollhardt, K P. C. (1977) *Accts. Chem Res.*, 10, 1.

134. Khand, I. U., Knox, G. R., Panson, P. L., Watts, W. E. and Foreman, M. I. (1973) *J. Chem. Soc., Perkin Trans.*, 1, 977.

135. Tsuji, J., Shimizu, I., Suzuki, H. and Naito, Y. (1979) *J Am. Chem. Soc.*, 101, 5070.

136. Funk, R. L. and Vollhardt, K. P. C. (1979) *ibid.*, 101, 215.

137. Exon, C. and Magnus, P. (1983) *ibid.*, 105, 2477.

138. Pearson, A. J. and Ong, C W. (1981) *ibid.*, 103, 6686.

139. Semmelhack, M. F. and Yamashita, A. (1980) *ibid.*, 102, 5924.

140. Ziegler, F. E. and Piwinski, J. J. (1982) *ibid.*, 104, 7181.

141. Evans, D. A. and Golob, A. M. (1975) *ibid.*, 97, 4765.

142. Lehmkuhl, H. (1981) *Bull. Soc. Chim. Fr., Part II*, 87. Oppolzer W. Pittelou, R. and Strauss, H. F (1982) *Tetrahedron Letts.*, 4669.

143. Oppolzer, W. and Battig, K. (1982) *Tetrahedron Letts*, 4669

144. Paquette, L A, Andrews, D R. and Springer, J. P. (1983) *J. Org. Chem.* 48, 1149.

145. Nicolaou, K. C, Petsis, N. A. and Zipkin, R. E. (1982) *J. Am. Chem. Soc.*, 104, 5560 and earlier papers in the series

146. Seebach, D (1979) *Angew. Chem. Int. Ed. Engl*, 18, 239.

147. Greene, T. W. (1981) *Protective Groups in Organic Synthesis* Wiley, J. and Sons New York, Mc Omie, J. F. W. (1973) *Protective Gropus in Organic Synthesis*, Plenum Press, New York

148. Starks, C. M. and Liotta, C. (1978) *Phase Transfer Catalysis* Academic Press, New York, Weber, W. P. and Gokel, G. W. (1977) *Phase Transfer Catalysis in Organic Synthesis*, Springer-Verlag Berlin.

149. Seebach, D and Corey, E. J. (1975) *J. Org. Chem.*, 40, 231.

150. Baldwin, J. E., Hofle, G A. and Lever, O. W. Jr. (1974) *J. Am. Chem. Soc*, 96, 7125.

151. Ranganathan, S, Ranganathan, D. and Mehrotra, A. K. (1974) *ibid.*, 96, 5261.

152. Seebach, D. and Meyer, N (1976) *Angew. Chem Int. Ed. Engl.*, 15, 438.

153. Manas, A. R. B. and Smith, R. A J. (1975) *J. Chem. Soc. Chem. Comm.*, 216.

154. Brinkmeyer, R S. and Kapoor, V. M. (1977) *J. Am. Chem. Soc.*, 99, 8339.

155. Noyori, R., Tomino, I. and Taminoto, J. (1979) *ibid.*, 101, 3129.

156. Mukaiyama, T. (1981) *Tetrahedron*, 37, 4111.

157. Vineyard, B. D., Knowles, W. S, Sabacky, M. J., Bachman, G. L. and Weinkauff, D. J (1977) *J. Am. Chem. Soc.*, 99, 5946.

158. Katsuki, T. and Sharpless, K. B. (1980) *ibid*, 102, 5974.

159. Katsuki, T., Lee, A. W. M., Ma, P., Martin, V. S., Masamune, S., Sharpless, K. B., Tuddenham, D. and Walker, F. J. (1982) *J. Org. Chem.*, 47, 1373.

160. Eliol, E L and Soai. K. (1981) *Tetrahedron Lett.* 22, 2859.

161. Woodward, R. B. in Todd, A. R. (Ed.) (1956) *Perspectives in Organic Chemistry* Interscience, New York.

162. Lin, Y. Y., Risk, M, Ray, S. M., Engen, D. V., Clardy, J., Golik, J., James, J. C. and Nakanishi, K. (1981) *J. Am. Chem. Soc.*, 103, 6773.

163. Corey, E. J (1971) *Quart. Rev.*, 25, 445.

164. Dev, S. (1983) *Proc. Indian Natn. Sci. Acad.*, 49A, 359.

165. Karady, S., Amato, J. S, Reamer, R. A. and Weinstock, L. M. (1981) *J. Am. Chem. Soc.*, 103, 6765.